Health Risk Assessment of Malathion Coproducts in Malathion-Bait Used for Agricultural Pest Eradication in Urban Areas

Supplemental to:

Health Risk Assessment of Aerial Application of Malathion-Bait
California Department of Health Services
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Prepared by:

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1.0 Executive Summary

Potential human health risks due to the aerial application of malathion-bait have been evaluated on several occasions. One of the more recent and most comprehensive health assessments is the 1991 document prepared by the Office of Environmental Health Hazard Assessment (OEHHA), California Environmental Protection Agency (Cal/EPA), then part of the California Department of Health Services (DHS), entitled: *Health Risk Assessment of Aerial Application of Malathion-Bait* (referred to throughout this document as *1991 HRA*). The *1991 HRA*, along with its predecessors, addressed the potential health impacts of exposure to malathion and malaoxon as the primary constituents of the malathion-bait mixture, but only superficially addressed exposure to other chemical components. The current risk assessment: *Health Risk Assessment of Malathion Coproducts in Malathion-Bait Used for Agricultural Pest Eradication in Urban Areas,* is intended to supplement the *1991 HRA* by addressing the risk from exposure to other chemical components of the malathion-bait mixture by evaluating the potential health impacts from exposure to malathion "coproducts," a group of chemicals present in all malathion technical mixtures including those used for the preparation of the malathion-bait mixture for aerial applications. Specifically, this work is intended to:

1) survey the toxicity of selected malathion coproducts and to evaluate the public health hazard potential of exposure to these compounds in malathion-bait,

2) assess the need for additional monitoring activities by the Department of Pesticide Regulation, and

3) determine if any of the conclusions in the *1991 HRA* require revision.

To accomplish these goals, all relevant toxicology, fate and chemistry literature was obtained by the Occupational and Environmental Health Library (OEHL) and was reviewed by staff of the Pesticide and Environmental Toxicology Section (PETS) of OEHHA. This literature review along with the results of the environmental monitoring served as the basis for the selection of indicator chemicals for this risk assessment. The coproducts isomalathion, trimethyl phosphorothioate [OOS(O)], and diethyl fumarate were selected as the most representative "indicator chemicals" for evaluation.

Environmental monitoring for malathion, malaoxon, and for five malathion coproducts was performed by staff of Cal/EPA's Hazardous Materials Laboratory (then part of DHS) over a nine-day period in May of 1990, encompassing the application over the city of Garden Grove. The results of the mass deposition monitoring are used in this risk assessment to estimate human exposure point concentrations of two of the three indicator chemicals [isomalathion and OOS(O)] in soil, water, and homegrown produce. Human exposure to the coproduct diethyl fumarate is calculated directly and solely from the mass deposition data. Concentrations of

OOS(O) in air were monitored and the results are used in this risk assessment for the estimation of dose. Problems were encountered during the isomalathion analysis and therefore air monitoring results for isomalathion are not available. This was apparently the result of the highly variable and low recovery rates from spiked samples. These problems were serious enough to prompt the authors to report the data as "qualitative only." No further explanation was provided regarding the source of the recovery problems. Therefore, for the purposes of this risk assessment, air monitoring results for malaoxon are used as surrogates for the inhalation component of the isomalathion dose. The mean and the upper 98^{th} percentile coproduct concentrations are calculated for each of the four environmental media (air, soil, water, and produce) which are then used for the estimation of human exposure at both the mean and upper 98^{th} percentile environmental concentrations.

Two "worst case" exposure scenarios are evaluated in this risk assessment; one for adults and one for children. These scenarios were selected from the *1991 HRA* because the occupation(s) and/or lifestyle(s) associated with these scenarios represented the members of the population receiving the greatest exposure for each age group. The hypothetical individuals modeled in this risk assessment can be considered equivalent to the maximally exposed individual, or MEI, used in risk assessments performed according to "Superfund" guidelines (U.S. EPA, 1989). By definition, the MEI is a hypothetical individual who represents the member of the population whose lifestyle results in their receiving the greatest exposure. For example, this risk assessment uses a hypothetical adult who might spend nearly all of their waking hours out of doors. Due to this increased opportunity for contact with contaminated surfaces, contaminated water and with the bait itself, this individual would receive a considerably greater exposure than would a sedentary office worker (who is at or near the opposite end of the "exposure spectrum"). An analogous situation exists in the scenario evaluated for children. In addition to the two complete scenarios, six (two adult and four child) special case situations are also evaluated as they were in the *1991 HRA*. For both age groups, the special cases of swimming in contaminated water and direct deposition of malathion-bait onto the skin are evaluated. For children, two additional special situations are evaluated: a case of pica and a case of direct malathion-bait consumption.

As is the case for all health risk assessments, assumptions are necessarily made in order to evaluate the chosen scenarios. For quantitative risk assessment, specific numerical values are required for parameters such as time spent outdoors, time spent swimming, body weight, and fruit and vegetable consumption, to name a few. As was the case for the *1991 HRA*, in the absence of any widely accepted risk assessment default assumptions, the values used are selected in order to maximize the estimated human doses. These assumptions would tend to overestimate actual dose levels and are therefore considered "health-protective."

The dose level estimates are compared against a reference exposure level (REL) specific for that coproduct. An REL is a level of exposure to the toxicant at which no adverse effects are anticipated. For the evaluation of risk of the non-carcinogenic, acute toxic effects of a particular compound, the hazard index is employed. The hazard index is calculated as the ratio of estimated dose to the REL. Health protection is achieved if the estimated or actual human dose level of coproduct is below the relevant REL, or if the hazard index is less than one. Exposures greater than the REL (hazard index is greater than one), are not necessarily hazardous and do not absolutely result in adverse health effects. However, further examination of the public health implications of such a result is required.

Based on our assessment, we conclude that following nighttime aerial applications of malathion-bait, as implemented by the California Department of Food and Agriculture (CDFA) in programs to eradicate exotic fruit flies, most individuals would not be expected to develop any adverse health effects from exposure to the coproduct isomalathion. However, due to analytical problems and limitations in the toxicological data base, considerable uncertainty is associated with the exposure estimates. As previoulsy discussed, air monitoring results for isomalathion are not available. In addition, although used in this risk assessment, inhibition of acetylcholinesterase (AChE) for isomalathion risk evaluation may not be the most appropriate toxicological endpoint. The indirect potentiation of malathion toxicity by the inhibition of carboxylesterases appears to be a very important toxicological effect of isomalathion. However, no methodology currently exists to quantify this effect for the purposes of risk assessment. Even with the use of a well-characterized endpoint such as inhibition of blood AChE, lack of toxicology data preclude the calculation of an isomalathion-specific REL. Therefore, an REL of 2,000 ng/kg-day for the endpoint of statistically significant inhibition of blood AChE developed for malaoxon in the *1991 HRA* is used in this risk assessment.

A comparison of the hazard indices for isomalathion alone with those for malaoxon and isomalathion combined, demonstrates an apparent minor role for isomalathion in the overall risk of AChE inhibition due to the aerial application of malathion-bait. For example, in the case of the representative child (#1 Child exposed at the 98th percentile environmental concentrations), summing the hazard index for AChE inhibition due to acute exposure to malathion (hazard index=16.2; from the *1991 HRA*, Table 8-4, page 8-24) to those from malaoxon and isomalathion (combined hazard index = 1.7; Table 5-3, this document) results in a hazard index of 17.9. Less than 2% of the total hazard index is due to isomalathion (hazard index = 0.32) alone. In all of the scenarios including special cases, there are no instances where the isomalathion component of the combined isomalathion/malaoxon hazard index exceeds 20%.

Complete scenario hazard indices for OOS(O), a representative of the class of compounds known as trialkyl phosphorothioates, range from 0.01 for the adult exposed to mean exposure point concentrations to 0.15 for the child exposed at the 98th percentile environmental concentrations. For the special cases, hazard indices range from 0.0003 for the pica child (mean exposure) to 0.08 for a child who swims in water contaminated at the 98th percentile concentration on the day of malathion-bait application. Based on these results, we conclude that following nighttime

aerial applications of malathion-bait, as implemented by CDFA in programs to eradicate exotic fruit flies, most individuals would not be expected to develop any adverse health effects from exposure to the coproduct OOS(O). O,O,S-trimethyl phosphorothioate is one of the more potent and frequently detected members of the trialkyl phosphorothioates in malathion formulations. Therefore, because the calculated hazard indices are well below 1.0 for OOS(O), it is concluded that most individuals would not be expected to develop any adverse health effects, including the observed pulmonary morphological changes, from exposure to any of the trialkyl phosphorothioates in malathion formulations.

Non-immunologic contact urticaria (NICU) is associated with exposure to diethyl fumarate. The risk assessment of exposure to diethyl fumarate in malathion-bait is included because of complaints of skin rashes during the 1989-90 Medfly eradication program in Los Angeles. Because NICU is a localized, non-systemic effect, exposure to this coproduct is quantified and evaluated as a "surface dose" rather than as an internalized or absorbed dose. Evaluation of the toxic potential of a hypothetical exposure using the hazard index approach suggests that diethyl fumarate is not a major factor in the production of skin disorders following malathion-bait applications; the REL is 80 ng/cm^2, the highest estimated dose is 19.4 ng/cm^2, resulting in a hazard index of 0.24.

A closer evaluation suggests that the hazard index may not be an appropriate means for evaluating the toxic potential of "surface doses" of locally-acting chemicals (e.g., diethyl fumarate). An estimated surface dose well below the hazard index can still result in a toxic response, since it is a concentration averaged across a given surface (e.g., the body), and could potentially obscure localized areas with high, low and even "no" concentrations. If the areas of high concentration exceed the REL, a toxic response may occur, even though the average concentration across the body surface may be quite low. Considering the sticky nature of the bait (which likely results in an elevated adherence factor), and the types of activities associated with the complaints (gardening and other behaviors with a high contact potential to a relatively small portion of the body surface), diethyl fumarate might contribute to the etiology of rashes subsequent to aerial applications of malathion-bait.

Several recommendations were developed as a result of this risk assessment:

(a) Improvement in analytical methodologies, particularly those needed for isomalathion monitoring, is important, as they are one of the most significant limiting factors in this risk assessment. Once the analytical methodology is improved, additional isomalathion monitoring to confirm or to modify the conclusion(s) of this report should be considered.

(b) Repeating the monitoring of diethyl fumarate on surfaces over a longer time period is suggested. Surface concentrations of this analyte continued to increase over the course of the monitoring activities. In some cases, surface levels showed

no evidence of tapering off, even after nine days. Air levels also persisted for some time after the application.

(c) Both surface and air monitoring for all analytes over a longer time frame with particular emphasis on repeated applications in order to estimate subchronic and/or chronic doses should be considered.

(d) Continue routine monitoring of malathion product and tank mixtures for the purposes of quantifying isomalathion. In accordance with the WHO recommendation, technical mixtures with isomalathion at levels exceeding 1.8% of the nominal malathion content should be rejected and returned.

(e) Close attention should be paid to the emerging toxicological literature as it pertains to malathion coproducts. This is especially important with respect to the trialkyl phosphorothioate class of coproducts because of the nature of the toxicity associated with exposure to these compounds (i.e., changes in lung morphology and fetal deaths in experimental animals). Since respiratory problems have been reported in malathion-bait exposed human populations, additional studies (toxicological, epidemiological, mechanistic) concerning the possible role of this class of coproducts in the etiology of these respiratory problems should be considered.

(f) Risk assessment methodologies pertaining to surface dose estimation should be reviewed and if necessary refined. Applicable research of surface to surface transfer rates, surface distribution profiles, and other exposure-related variables is important in order to more accurately evaluate the toxic potential of exposure to locally acting, topically active agents. Additional areas for research may be identified during routine literature reviews.

(g) Information concerning the environmental persistence and fate of all coproducts would be important to derive a more realistic estimate of chronic human exposure to malathion coproducts. Studies regarding the environmental behavior of these compounds would help to reduce the uncertainty in chronic exposure assessment.

(h) Exposure to malathion coproducts over a period of several days to weeks due to repeated bait applications over the same area(s) is plausible. A greater understanding of the longer term toxicities of the coproducts would aid the evaluation of potential risks from this type of exposure. There are few sub-chronic and chronic toxicity tests for the coproducts of malathion; results from such studies would be helpful to characterize the risks of repeated exposure to these compounds.

2.0 Introduction

2.1 Recent History of Malathion Bait Use for Medfly Eradication

On numerous occasions, aerial application of a malathion and protein bait mixture has been utilized in Mediterranean Fruit Fly ("Medfly") and other exotic fruit fly eradication programs in California. A detailed history of the use of malathion-bait for this purpose is provided elsewhere (DHS, 1991a). Malathion-bait applications are still a prominent tool used in this state against the Medfly. Applications occurred as recently as March of 1995, encompassing a predominantly semi-rural area of approximately 15 square miles.

For Medfly eradication programs prior to the February 1994 aerial application over Corona, malathion was formulated at a nominal concentration of 20% by weight malathion with an acid-hydrolyzed corn-gluten bait. The bait mixture is a dark brown, slightly viscous, proteinaceous liquid consisting of approximately one-half solids (dry weight), one-quarter protein, and one-quarter salts, carbohydrates, sugars and fat. The 20% malathion formulation was in use during the deposition monitoring for both the *1991 HRA* and this document, thus the exposure estimates derived in both documents are relevant to the application of 20% malathion. Since February 1994, however, the malathion concentration in the malathion-bait mixture was reduced to 10%, thus the dose estimates derived in both the *1991 HRA* and in this document are presumably up to two times greater than they would be if they were based on monitoring data from the most recent applications.

Public concern arises when these applications occur over densely populated areas, exposing potentially large numbers of individuals to not only malathion and malaoxon but to other constituents of the malathion technical mixture as well. During 1989/1990, a series of malathion-bait applications were conducted in the Los Angeles basin, one of the most densely populated, urbanized areas of the state. Applications occurred over a 595 square mile area, affecting four counties and exposing potentially 1.5 million residents to materials contained in the malathion technical mixture. This widespread application triggered a great deal of public outcry and concern.

The California Department of Health Services (DHS) responded to this public reaction with the initiation of a "state-of-the-art" health risk assessment. This health evaluation of aerial malathion-bait application, entitled *Health Risk Assessment of Aerial Application of Malathion-Bait* (referred to subsequently as *1991 HRA*) was completed in February 1991 (DHS, 1991a). The *1991 HRA*, as were previous health evaluations of malathion-bait applications, was limited to malathion and malaoxon as the primary constituents in the bait mixture and only superficially addressed exposure to other chemical components. The lead organization for the preparation of the *1991 HRA*, the Office of Environmental Health Hazard Assessment (OEHHA), under a 1993 memorandum of understanding, was asked by DHS to evaluate the potential health effects from exposure to these coproducts following aerial malathion-bait application. Accordingly, the present risk assessment, entitled *Health Risk Assessment of Malathion Coproducts in Malathion-*

Bait Used for Agricultural Pest Eradication in Urban Areas, provides additional information regarding the potential health effects from exposure to other materials found in the malathion technical mixture. The specific objectives of this document are to:

(1) survey the toxicity of selected malathion coproducts and to evaluate the public health hazard potential of exposure to these compounds in malathion-bait,

(2) assess the need for additional monitoring activities by the Department of Pesticide Regulation, and

(3) determine if any of the conclusions in the 1991 DHS Risk Assessment require revision.

2.2 Constituents of Malathion Technical Mixtures

Numerous compounds are found in technical grade formulations of pesticides. Although some of these compounds or "coproducts" are simply breakdown or conversion products of the active ingredient, the majority arise from unintentional reactions occurring during synthesis of the pesticide. Some coproducts, such as isomalathion, can be formed via both mechanisms. At least 11 chemicals, in addition to the active ingredient, are routinely detected in malathion technical mixtures and are considered malathion coproducts. Relative to the active ingredient malathion, these coproducts are present in small amounts; individual concentrations range from barely detectable (or less) to approximately 1% of the nominal malathion concentration. Although never encountered in the California exotic fruit fly eradication program, severely contaminated batches are occasionally reported. For example, technical mixtures stored for extended periods under warm, humid conditions may contain isomalathion at concentrations as high as 7%. More typically, however, the total coproduct concentration in a malathion technical mixture is less than 5%. The major coproducts found in technical grade malathion concentrates, along with their "representative" concentrations, are as follows (1991 *HRA; Brown et al.*, 1993 - data supplied by manufacturer):

isomalathion	0.20%
malaoxon	0.10%
diethyl fumarate	0.90%
O,S,S-trimethyl phosphorodithioate [OSS(O)]	0.003%
O,O,S-trimethyl phosphorothioate [OOS(O)]	0.04%
O,O,S-trimethyl phosphorodithionate [OOS(S)]	1.2%
O,O,O-trimethyl phosphorothionate [OOO(S)]	0.45%
diethyl hydroxysuccinate	0.05%
ethyl nitrite	0.03%
diethyl mercaptosuccinate	0.15%
diethyl methylthiosuccinate	1.0%

The above coproduct concentrations are only examples of what may be found in a given batch of technical malathion. The concentration of individual coproduct varies from batch to batch, as does the total coproduct concentration. Concentrations of coproducts found in tank mixes can be different form those shown above.

2.3 Selection of "Indicator Chemicals"

Approximately 60 research articles regarding the toxicity and chemical analysis of malathion coproducts were identified and retrieved by staff as a result of a comprehensive literature search. Review of these articles in light of the available monitoring data (supplied by Hazardous Materials Laboratory staff), provided the basis for the selection of specific coproducts for evaluation, a necessary task as the coproducts are too numerous to realistically monitor during and to evaluate following a malathion-bait application. Even if monitoring for all coproducts were practical, the usefulness of the data for risk assessment purposes would be limited since adequate toxicology data are not available for the majority of these chemicals.

Because of these practical limitations, in order to assess the health risks associated with exposure to coproducts in malathion technical mixtures, the selection of representative or "indicator chemicals" is necessary. The use of indicator chemicals assumes that the majority of exposure and health risks would be accounted for by the selected chemicals and that the exposure and/or health effects of the remaining chemicals are relatively insignificant.

The selection process for indicator chemicals used in this risk assessment considered the inherent toxicity of the coproduct, its percent composition in the technical mixture, and the availability of toxicity information and monitoring data. Using these criteria, the following coproducts were selected for quantitative evaluation and inclusion in this document:

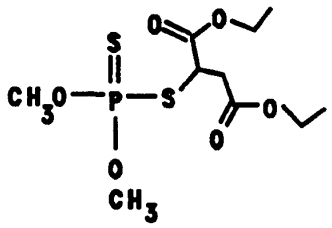
ISOMALATHION: The acute mammalian toxicity of any given "batch" of technical malathion is increased by the presence of this coproduct. It is known as one of the most potent potentiators of malathion toxicity. In addition, isomalathion inhibits acetylcholinesterase (AChE) with a potency similar to that of malaoxon, and is present in relatively high concentrations compared to other coproducts in technical mixtures of malathion.

DIETHYL FUMARATE: This coproduct is a known causative agent of non-immunologic contact urticaria (NICU) in humans. Skin irritation and rashes have been reported following malathion-bait application(s), both of which are symptomatic of NICU. Accordingly, characterization of the exposure potential to this material is important.

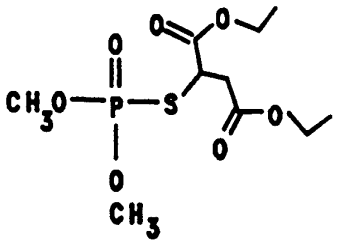
O,O,S-TRIMETHYL PHOSPHOROTHIOATE [OOS(O)]: This coproduct is a representative of an important chemical class of coproducts, the trialkyl phosphorothioates (TAPTS). It is the only member of this group for which

monitoring and suitable toxicity data are available. Although the toxicity data are limited, it is sufficient for the purposes of this risk assessment.

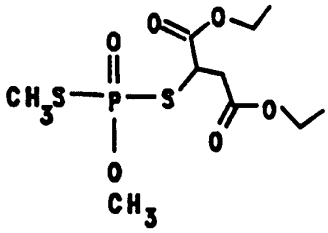
The structures of the three indicator chemicals are shown in Figure 1, along with the structures of malathion and malaoxon.



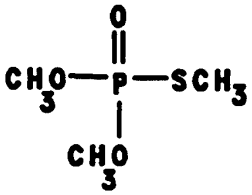
malathion



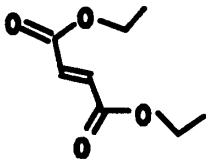
malaoxon



isomalathion



O,O,S-trimethyl phosphorothioate [OOS(O)]



diethyl fumarate

Figure 2-1. Structures of malathion, malaoxon, isomalathion, O,O,S-trimethyl phosphorothioate and diethyl fumarate.

3.0 Toxicity Profiles for "Indicator Chemicals"

3.1 Toxicity Profile for Isomalathion

3.1.1 Introduction

Isomalathion (O,S-dimethyl-S-(1,2-dicarboethoxy)ethylphosphoro-dithioate) is a contaminant common to all malathion technical grade mixtures and formulations, as it is formed during both the manufacture of the technical product and storage of either the technical mixture or formulation. Technical grade malathion contains approximately 92 to 98% parent compound; the remainder being coproducts and/or "breakdown products." Although concentrations of isomalathion relative to malathion in technical mixtures are generally quite low (rarely exceeding 0.5% of the nominal malathion content), it is one of the most predominant contaminants found in the technical mix. Upon storage, isomalathion content increases due to isomerization of malathion to isomalathion. This conversion is most prone to occur in malathion formulations, especially water dispersible powders[1], where levels exceeding 3.0% are common (Halder and Parmar, 1984; Miles *et al.*, 1979; Rengasamy and Parmar, 1988). The extent of isomerization is a function of storage conditions (temperature, relative humidity, and storage time) and, in the case of formulations, the type of carrier used. Of the commercially important carriers, only silica gel-G and hydrated calcium silica appear to prevent the formation of isomalathion.

3.1.2 Cholinesterase Inhibition

Like malaoxon, the active metabolite of malathion, isomalathion is a direct inhibitor of cholinesterase requiring no metabolic activation to exert its toxic action. However, there are few reports available in the literature that describe the direct inhibition of cholinesterase by isomalathion (Clothier *et al.*, 1981; Talcott *et al.*, 1979a; Thompson *et al.*, 1989). Structurally, isomalathion is nearly identical to malaoxon, the active form of malathion. Substitution of sulfur for a methoxy-oxygen in malaoxon yields isomalathion. The similarities hold toxicologically as well. A comparison of LD_{50} values for the rat following oral exposure reveals that isomalathion and malaoxon are essentially equipotent (isomalathion LD_{50} = 113 mg/kg; Rengasamy and Parmar, 1989: malaoxon LD_{50} = 158 mg/kg; Aldridge *et al.*, 1979).

3.1.3 Potentiation of Malathion Toxicity via Inhibition of B-type Carboxylesterases

Perhaps the most important toxic effect of isomalathion is the potentiation of malathion toxicity. The mechanism of this potentiation is thought to be the inhibition of B-type carboxylesterases (CEBs), the group of enzymes responsible for the metabolism of malathion into the relatively non-toxic *alpha* and *beta* monoacids of malathion and malaoxon. Even though CEBs are found in essentially all tissues, those found in the blood and liver are quantitatively the most important

[1] Water dispersible powders are not used in California for malathion-bait mixtures used in exotic fruit fly eradication programs.

in the breakdown of malathion (Rabovsky and Brown, 1993). Malathion-carboxylesterases are not found in insects. Therefore, a significantly greater proportion of the absorbed malathion dose is available for activation into malaoxon in insects than in those species possessing CEB activity. This metabolic difference is generally regarded as being responsible for the selectivity of malathion towards insects (Cassarett and Doull, 1986). Inhibition of CEBs in resistant species will render them more susceptible to the toxic effects of malathion. Several coproducts found in the malathion technical mixture, in particular isomalathion and some of the trialkyl phosphorothioates (e.g., OSS(O), OOS(O), and OOS(S), are potent CEB inhibitors). The $LD_{50(rat,oral)}$ is significantly lowered by the presence of these compounds in the technical mixture. Early work by Pellegrini and Santi (1972) demonstrated that purification of a malathion technical mixture via recrystalization could raise the $LD_{50(rat,oral)}$ five-fold (1,580 mg/kg for the technical mixture; 8,000 mg/kg for purified malathion). This change in mammalian LD_{50} occurred with no alteration in its insecticidal properties.

A survey of the malathion scientific literature reveals a wide range of values published as "the $LD_{50(rat,oral)}$" of malathion. Prior to 1972, the $LD_{50(rat,oral)}$ of technical malathion was considered to be in the range of 1,000 to 2,000 mg/kg (see Aldridge *et al.*, 1979 and references therein). Today, the modifying potential of contaminants in technical mixtures is well established, as several examples of potentiation of toxicity by contaminants in technical mixtures are known, most of which involve the organophosphates. The $LD_{50(rat,oral)}$ of the malathion technical mixture is dependent upon the types and amounts of contaminants present, while the $LD_{50(rat,oral)}$ of pure malathion is approximately 10,000 to 12,000 mg/kg (Aldridge *et al.,* 1979; Fukuto, 1983; Iyer and Parmar, 1984; Miles *et al.,* 1979; Verschoyle *et al.,* 1982).

Supporting evidence of the unique role of isomalathion in the mammalian toxicity of technical grade malathion is found in a report of an epidemic of malathion poisoning that occurred among Pakistani malaria workers in 1976 (Baker *et al.,* 1978). Approximately 7,700 workers were potentially exposed. Based on the frequency of symptoms in the surveyed workers (approximately 8% of the 7,700 workers received questionnaires), there may have been 2,800 cases with at least one episode of pesticide intoxication, as well as possibly five deaths. However, there was no control population to compare background occurrence of these symptoms in unexposed workers. This reported epidemic was a direct result of the use of an acutely toxic organophosphate made more toxic by the presence of elevated amounts of isomalathion. These workers were previously trained and experienced in handling less acutely toxic organochlorines. However, the authors observed improper work practices in the use of the malathion formulations. Three different batches of malathion-water dispersible powder were in use at the time, the analysis of which revealed isomalathion concentrations ranging from 0.3 to 3.1% of the malathion content. An inverse correlation ($r = -0.83$) was demonstrated between isomalathion content of the malathion batch used and the red blood cell cholinesterase (RBC-ChE) activity in blood samples drawn from field personnel during the episode. No correlation was observed when comparing the RBC-ChE activity with the concentrations of other contaminants (e.g., the trialkyl phosphorothioates). That isomalathion content is proportional to enhanced toxicity of malathion technical mixtures while concentrations of other contaminants are not is consistent

with observations in the rat (Aldridge *et al.,* 1979). The data provided in this publication are insufficient for use in quantifying isomalathion's potentiation of malathion mammalian toxicity, and therefore are used for qualitative purposes only.

Partially in response to the Pakistan incident, the World Health Organization promulgated standards regarding isomalathion content of malathion-water dispersible powder after an accelerated storage test. The World Health Organization recommends that any malathion-water dispersible powder formulation that contains isomalathion at a concentration exceeding 1.8% of the nominal malathion concentration be discarded and not used (WHO, 1978). Even though water dispersible powder formulations are not used in California exotic fruit fly eradication programs, malathion batches used in these programs are routinely screened for the presence of isomalathion. As expected, isomalathion concentrations have been found to be quite low (less than 0.2% of the nominal malathion concentration). Nevertheless, according to CDFA, any batches found to contain isomalathion at levels exceeding 1.8% will be discarded.

As stated earlier, in addition to isomalathion, several other contaminants present in "malathion" products are also CEB inhibitors and may contribute to the potentiation of malathion toxicity in mammals. The most important of these are the trialkyl phosphorothioates (TAPTs) whose inhibitory actions towards CEB are well known. The relative potency of the TAPTs in inhibiting CEB are: OSS(O) > OOS(O) > OOS(S). This relationship has been demonstrated *in vitro* by a number of investigators: in rat serum (Mallipudi *et al.,* 1980; Talcott *et al.,* 1979b), in rat, rabbit, and porcine liver preparations (Malik and Summer, 1982; Mallipudi *et al.,* 1980; Lin *et al.,* 1984), as well as *in vivo*: in rat liver (Ryan and Fukuto, 1984; Talcott *et al.,* 1979a), and in serum and blood (Ryan and Fukuto, 1984). When evaluated in these assays, isomalathion is equally as or more potent than OSS(O) as a CEB inhibitor. For example, isomalathion is approximately 100 times more potent than OSS(O) in inhibiting rat serum CEB *in vitro*. The concentrations required to produce 50% enzyme inhibition (IC_{50}) were 0.0005 mM and 0.04 mM for isomalathion and OSS(O), respectively (Aldridge *et al.,* 1977). On the other hand, these two chemicals possess comparable potency in their ability to inhibit CEB activity in isolated rat hepatocytes (Malik and Summer, 1982). One hour after exposure to either isomalathion or OSS(O) at 0.03 mM, isolated rat hepatocytes displayed 27% or 18%, respectively, of the CEB activity observed in the controls.

Malathion CEB activity in human liver samples obtained at autopsy was investigated by Talcott *et al.* (1979b). These investigators, utilizing a partially purified human liver CEB preparation, sought to determine IC_{50}s for OOS(S), OOS(O), OSS(O), and isomalathion. Even at the highest concentration tested (7.5 mM), these three TAPTs showed no inhibitory activity towards human liver CEB, *in vitro*. These limited data may indicate species differences in the dose-response for inhibition of CEB by TAPTs. Isomalathion was an effective inhibitor with an IC_{50} of 0.6 μM.

Several investigators have demonstrated potentiation of malathion toxicity by these CEB inhibitors (Aldridge *et al.,* 1979; Fukuto, 1983; Iyer and Paramar, 1984; Miles *et al.,* 1979; Pellegrini and Santi, 1972; Ryan and Fukuto, 1985; Umetsu *et al.,* 1977). This potentiation or increased sensitivity to malathion is typically measured as a decrease in the malathion LD_{50}. With this measurement of potentiation, OSS(O) appears to be the most active TAPT potentiator of malathion toxicity, at least in the rat.

Humans possess very limited blood CEB activity compared to rodents, thus rendering the liver as the primary site of malathion degradation in humans (Rabovsky and Brown, 1993). Hepatic enzymes play a lesser role and blood CEBs appear to be the primary esterases responsible for malathion degradation in rodents. If the result in which isomalathion was the only inhibitor of human hepatic CEBs *in vitro* is also true *in vivo*, it would suggest that isomalathion is the most significant coproduct of malathion with regard to human toxicity. This possibility would explain the correlation between blood cholinesterase depression in Pakistani malaria workers and isomalathion content (but not with any of the other coproducts) of the specific malathion batch in use (Baker *et al.,* 1978). This is also consistent with the observation in rodents that the combination of pure malathion and pure isomalathion results in a degree of potentiation less than that from a technical mixture with an identical isomalathion content (Aldridge *et al.* 1979). Therefore, although it is likely that all CEB inhibitors contribute to potentiation of malathion toxicity to varying degrees and with species dependency, isomalathion is apparently the most important coproduct with regard to human toxicity, and humans appear to be more sensitive to the potentiation of malathion toxicity by isomalathion than the other species tested.

No quantitative methodologies are available at the present time to evaluate potentiation of malathion toxicity in a manner suitable for risk assessment. Therefore, the inhibition of AChE is used for the evaluation of risk due to isomalathion exposure.

3.1.4 Determination of Acute Reference Exposure Level

Little information is available in the scientific literature concerning the inhibition of AChE by isomalathion. However, the toxicological and chemical properties of isomalathion are comparable to malaoxon. This is most likely the result of the structural similarities between the two compounds, in particular the P=O "double bond." Therefore, the acute REL based on statistically significant inhibition of blood AChE by malaoxon (developed in the *1991 HRA*) is used for the purposes of this risk assessment as an approximation of an REL for isomalathion, and as a sensitive indicator of isomalathion toxicity in humans. In deriving the REL for malaoxon, a NOAEL of 0.23 mg/kg-day was used for statistically significant inhibition of blood AChE by malathion (significance was defined as AChE inhibition of greater than 10%) as identified in human volunteers by the study authors Moeller and Rider (1962). An uncertainty factor of 100 was applied to this NOAEL to account for variability among humans and for the approximately 10-fold greater potency of malaoxon compared to malathion. This yielded an REL of 0.002 mg/kg-day for malaoxon, and for use in this risk assessment, for isomalathion.

Additional details regarding the derivation of this acute REL can be found in the *1991 HRA*, pages 8-11 through 8-13.

3.2 Toxicity Profile for O,O,S-Trimethyl phosphorothioate [OOS(O)]

3.2.1 Introduction

Trialkyl phosphorothioates are present as impurities in several technical grade organophosphorous products, including malathion. These compounds may arise as either side reaction products or breakdown products of the desired material. The TAPTs found in the highest concentrations are also the best characterized and are: O,O,O-trimethyl phosphorothionate [OOO(S)], O,O,S-trimethyl phosphorothioate [OOS(O)], O,O,S-trimethyl phosphorodithionate [OOS(S)] and O,S,S-trimethyl phosphorodithioate [OSS(O)]. In addition to these methyl esters, ethyl esters may be present in the technical mixture[2]. Mixed (methyl plus ethyl) esters may also be present in trace quantities in technical malathion. Their physical, chemical and toxicological properties are poorly characterized. These mixed esters are not further discussed in this section.

3.2.2 General Toxicity

3.2.2.1 Acute Toxicity and Potentiation of Malathion Toxicity

During an investigation of the potentiation of malathion toxicity by various impurities, it was found that storage of malathion with dimethyl phosphorothioates resulted in generation of TAPTs via the methylation of the diester by malathion (Verschoyle *et al.*, 1982). The TAPTs that were produced were found to be potent inhibitors of guinea pig plasma carboxylesterases, significant inhibition of which was achieved when concentrations of TAPTs in malathion reached 0.2 to 1% (w/w) (Verschoyle *et al.*, 1982). The potentiation of malathion toxicity by TAPTs, at least as observed in laboratory animals, appears to be the result of TAPT interference with malathion metabolism by carboxylesterase(s) (Imamura and Gandy, 1988; Aldridge *et al.*, 1979; Umetsu *et al.*, 1977).

Since malathion and related phosphate esters are cholinesterase inhibitors, one of the first effects of TAPTs studied was their ability to inhibit cholinesterase (Ryan and Fukuto, 1985; Clothier *et al.*, 1981). Cholinesterases are inhibited by TAPTs and the resulting phosphorylated enzyme can either be reactivated or "aged" (Clothier *et al.*, 1981). When large doses (260 mg/kg) of OOS(O) or OSS(O) are given to rats, early cholinergic signs are evident, including: fasciculations, salivation, urinary incontinence and sometimes chromodacryorrhea (Mallipudi *et al.*, 1979). At lower doses (15 to 80 mg/kg), these overt symptoms are not present, although cholinesterase

[2] In this document, ethyl esters are abbreviated similarly to the methyl esters, with the addition of the "ethyl" to the name. For example, the tri-ethyl analog of OOO(S) is identified as OOO-ethyl-(S).

activity is depressed (Mallipudi *et al.*, 1979). Even though cholinergic symptomatology was absent, rats receiving the lower doses died two to eight days after dosing (Mallipudi *et al.*, 1979; Aldridge and Nemery, 1984).

3.2.2.2 Delayed Toxicity

The condition in which rats die two to eight days (or longer) after exposure, with little or no cholinergic symptomatology, is referred to as "delayed toxicity." When administered to rats at 20 mg/kg, OOS(O) results in weight loss, moderate to heavy diarrhea or urination, cessation of food and water intake, and occasional staining of the mouth, nose and eyes (Hammond *et al.*, 1982). Pathological changes are seen prominently in the liver, and morphological changes are observed in the heart, adrenals, tissues of the small intestine and kidney, and significant bronchopneumonia is present. Death from a single dose of 15 mg/kg OOS(O) was reported to occur about 20 days after dosing (Fukuto, 1984). After four months of daily feeding of 2.5 or 5 mg/kg OOS(O) to rats, no significant weight loss or increase in deaths was noted. Daily administration of 10 mg/kg-day OOS(O) for four months resulted in weight loss and one death (out of four) (Fukuto, 1984). Atropine or the administration of nutritional supplements failed to ameliorate the illness (Umetsu *et al.*, 1981). However, the concomitant administration of OOO(O) was found to be a potent antagonist of the delayed toxicity of OOS(O) and OSS(O) (Fukuto, 1984; Imamura and Gandy, 1988). These authors speculated that OOO(O) may play an inhibitory role in the metabolic activation of OOS(O) and OSS(O).

In comparative studies of the "delayed toxicity" associated with some selected esters (Aldridge and Nemery, 1984), it was found that OOS(O) is one-half as toxic as its ethyl ester counterpart (LD_{50} of 60 compared to 27 mg/kg). OSS(O) was two times more toxic than OOS(O) (LD_{50} of 26 compared to 60 mg/kg). OOO(O) does not cause delayed toxicity. However, it is acutely toxic with an LD_{50} of greater than 1,000 mg/kg.

3.2.2.3 Miscellaneous Toxic Effects

Other effects have been noted in animals exposed to OOS(O) or OSS(O). Nemery (1987) reported metabolic alkalosis shortly after exposure to OSS(O) at a dose of 10 mg/kg. Other signs of nephrotoxicity included a four-fold increase in urine flow with increases in albumin, B2-microglobulin and N-acetyl glucosaminidase excretion. Another report indicated that rats administered 60 mg/kg OOS(O) showed severe hemoconcentration (Hammond *et al.*, 1982). No metabolic acidosis was reported, but plasma concentrations of Na^+ and Cl^- declined steadily over time.

Kidney damage induced by OSS(O) and OOS(O) was studied microscopically by Keadtisuke *et al.* (1989). They found substantial damage to the glomeruli by both compounds. However, the proximal tubule may be the site of initial damage since large amounts of amino acids, glucose, and low-molecular weight proteins were detected in the post-dosing urine samples.

Bezencon *et al.* (1989) studied hemorheological changes in rats treated with OOS(O). Whole blood viscosity, plasma fibrinogen content and red blood cell (RBC) aggregation increased in treated animals compared to controls. The authors felt that pathological and biochemical events associated with local lung injury might contribute to these changes as well as the possibility that OOS(O) might induce lower blood oxygen tension. These authors did not adequately investigate whether these changes were due to impaired kidney function.

The liver production of blood clotting factors is also damaged by OOS(O) and OSS(O), as evidenced by prolongation of blood clotting and increases in prothrombin and thrombin times (Keadtisuke *et al.*, 1990). Deficiency of factors II, V and VII was observed. Beta-glucuronidase in the blood was also increased.

3.2.3 Immunological Effects

The potential immunotoxicity of OOS(O) has been investigated (Devans *et al.*, 1985; Rodgers *et al.,* 1985a,b,c,d; Rodgers and Ellefson, 1990). These investigators found that acute oral administration of 10 mg/kg OOS(O) to mice (a dose without overt toxic signs) resulted in suppression of the generation of both cytotoxic T-lymphocytes and antibody-secreting cells. Macrophages from treated animals were in a higher state of activation, including increased levels of nonspecific esterases and an increase in size over control macrophages. Additionally, macrophages from treated animals did not exhibit tumoricidal activity (Rodgers *et al.*, 1985a,b). The state of macrophage activation was studied further by evaluating the levels of neutral proteases, which were transiently elevated upon treatment. Plasminogen activator and collagenases returned to normal levels within seven days, but elastase activity remained elevated (Rodgers and Ellefson, 1990). Interestingly, low dose treatment of mice with OSS(O) (0.5 mg/kg-day for 14 days) is associated with increased thymic lymphocyte weight and number and may possibly enhance certain humoral responses (Rodgers *et al.*, 1985c).

3.2.4 Pulmonary Effects

Pulmonary injury has been observed following experimental exposure to levels of OOS(O) and OSS(O) as low as 15 mg/kg. This toxicity requires several days post-TAPT exposure to develop. Upon gross examination, pulmonary toxicity is characterized by progressive interstitial thickening, loss of alveolar space, inflammatory cell infiltration, and debris found in the bronchioles (Dinsdale *et al.*, 1982). It has been argued that lung damage leading to hypoxia is responsible for the deaths observed in the cases of “delayed toxicity” due to TAPTs (Aldridge and Nemery, 1984; Immamura and Gandy, 1988). Significantly higher doses, approaching 260 mg/kg, are required for the production of renal and/or hepatic toxicity. Therefore, toxicity observed in these organs probably plays a minor role, if at all, in the etiology of “delayed toxicity” following TAPT exposure.

Microscopic evaluation indicates that the pulmonary injury involves several cell types. Type I cells are damaged, which probably induces the proliferation of Type II cells. The newly formed

type II cells are deficient in their content of lamellar bodies. Little damage to endothelial cells was reported with OSS(O) or OOS-ethyl-(O) (Aldrich and Nemery, 1984), whereas with OOS(O), endothelial cells were the initial cells affected (Imamura and Gandy, 1987). Upon dosing with OOS(O), rat lungs were found to have fewer and atypical appearing Clara cells (Imamura *et al.*, 1983). The Clara cells were devoid of granules, which are important for their secretory function. Note that this finding was not confirmed by another group, Verschoyle and Dinsdale (1990), who observed no effect on Clara cells.

Koizumi *et al.* (1988) investigated *in utero* exposure to OOS(O) and found that oral administration of single doses of 0.5, 2.5, 5, 10, or 40 mg/kg to pregnant rats resulted in increased fetal deaths compared to controls at doses of 2.5 mg/kg or greater. Histopathological examination of fetal pulmonary tissue revealed interstitial cell proliferation and delayed septal/capillary development, while in dams it showed a dose-related proliferation of pulmonary type II cells. These fetal and maternal pulmonary effects were seen at all doses studied. In a later study, this group investigated the production of pulmonary surfactant (disaturated phosphatidylcholine) in fetuses to determine if a deficiency of production could be associated with fetal toxicity (Koizumi *et al.*, 1989). An association was not demonstrated, as the doses at which surfactant decrease was significant were 7.5 and 20 mg/kg and not at 2.5 mg/kg, which is the lowest dose associated with increased fetal deaths.

3.2.5 Mechanism of Toxic Action

Metabolic activation of OOS(O) and OSS(O) is required to produce the moiety responsible for pulmonary toxicity, a conversion occurring in the lung (Nemery and Aldridge, 1988; Verschoyle and Dinsdale, 1990). Pulmonary cytochrome P-450 is selectively inhibited by OOS(O) compared to the liver enzyme. The metabolic inhibitor piperonyl butoxide is able to protect the lung (Imamura and Gandy, 1988), as does pretreatment with phenobarbital (Gandy *et al.*, 1983). The presence of sulfur appears to be a prerequisite for toxicity (Cardenas and Nemery, 1991). Oxidation of sulfur may lead to metabolites which bind to protein sulfhydryl groups leading to the production of protein disulfides (Nemery and Aldridge, 1988).

Another line of investigation has been to examine the role of alveolar macrophages, since their activation would produce free radicals of the type that would damage alveolar Type I cells (Imamura and Thomas, 1985). These researchers found that following exposure to TAPTs, protease inhibitor activity found in macrophages was reduced, therefore suggesting an increase in protease activity. They suspect that this lung protease, which is normally repressed, is activated upon treatment with TAPTs.

3.2.6 Derivation of Acute Reference Exposure Level

A single dose of 15 mg/kg of OOS(O), or repeated administration of 10 mg/kg-day OOS(O) for four months can be lethal to adult rats (Fukuto, 1984). The work of Koizumi (1988) shows that doses as low as 2.5 mg/kg-day, when given to pregnant rats, can be lethal to neonates. The authors concluded that this fetal mortality was due to the pulmonary injury caused by OOS(O). Sacrificing dams before giving birth reveals that both dams and fetuses have lung morphological changes at a dose of 0.5 mg/kg-day. Therefore, a LOAEL of 0.5 mg/kg-day for OOS(O) can be selected for the acute oral effect of pulmonary morphological changes. The acute REL is derived as follows:

$$\text{REL} = \frac{\text{LOAEL}}{(F1)(F2)(F3)} = \frac{0.5 \text{ mg/kg-day}}{(10)(10)(10)} = 0.000\,5 \text{mg/kg-day} = 500 \text{ ng/kg-day}$$

where:

F1 = uncertainty factor for intraspecies variation
F2 = uncertainty factor for interspecies variation
F3 = uncertainty factor to derive a NOAEL from a LOAEL

3.2.6.1 Uncertainties with the REL approximation

The toxicity database on these compounds is limited and standardized tests for long-term toxicity are virtually nonexistent. The LOAEL selected for derivation of the REL is based on the lowest dose tested experimentally. Additional work is needed to evaluate responses at lower doses utilizing more sensitive measures of effect.

The REL is determined for one TAPT only [OOS(O)] and cannot be used indiscriminately for the entire class. It is likely that when exposed to known TAPTs in malathion solutions, there is concomitant exposure to other TAPTs {e.g., OSS(O)} which have similar or perhaps greater toxicity than OOS(O). Other TAPTs {e.g., OOO(O)} would also be present that are less toxic and/or antagonize the toxicity of the more toxic TAPTs (Imamura and Gandy, 1988). Further work is necessary to quantify the nature of the interactions before any determination can be made for the group as a whole.

3.2.7 Conclusions

Trialkyl phosphorothioates are known to inhibit serine proteases, including cholinesterases and B-type carboxylesterases. More significantly, a few of these compounds induce death days after exposure, an effect apparently not associated with the inhibition of these enzymes. This “delayed toxicity” has been observed with OOS(O), OSS(O), and OOS-ethyl-(O) and may include other TAPTs which have not been tested. The prevailing belief is that pulmonary damage, particularly to cells in the alveolus as observed early post-dosing, is the cause of death. Although an increased incidence of mortality was not observed following exposure to 0.5 mg/kg of OOS(O),

pulmonary morphological changes qualitatively identical to those seen at doses resulting in an increased mortality were observed. This endpoint (pulmonary morphological changes) and dose (0.5 mg/kg) were used as the basis for the acute REL of 500 ng/kg determined for OOS(O).

3.3 Toxicity Profile for Diethyl Fumarate

3.3.1 Introduction

Diethyl fumarate (2-butenedioic acid diethyl ester; ethyl fumarate; CASRN 623-91-6) is used in the production of malathion and in the manufacturing of copolymerization products with such active monomers as styrene, vinyl acetate, acrylates, and ethylene (Lahti and Maibach, 1985a; Lewis, 1992). It is a white crystal or colorless liquid and has a molecular weight of 172.2 (Lewis, 1992; White and Cronin, 1984).

3.3.2 Toxicity

Little information is available on the toxicity of diethyl fumarate. It is described as moderately toxic by ingestion, with an acute oral LD_{50} in the rat of 1,780 mg/kg (Lewis, 1992).

The only other toxic effect reported in both humans and laboratory animals is non-immunologic contact urticaria (NICU). Contact urticaria is an erythema and edema reaction that appears 5 to 60 minutes after certain substances contact skin, and disappears within a few hours (Lahti and Maibach, 1985b). There appears to be two forms of contact urticaria, one involving the immune system and one that does not. Symptoms common to both forms include erythema and edema, and tingling, burning, or itching of the skin. With NICU, the most common form of urticaria, the intensity of the reaction depends on the substance, concentration, and skin site. All exposed species tend to exhibit comparable reactions which are localized and do not cause systemic symptoms. With immunologic contact urticaria, however, the intensity is only partially dependent upon the concentration of the causative agent. Mild immunologic contact urticaria reactions are fairly common but more severe ones, accompanied by generalized urticaria (hives), asthmatic attack and anaphylaxis, are rare (Lahti and Maibach, 1985b; 1985c; Lahti *et al.*, 1986; 1987).

Immunologic contact urticaria is an immediate allergic reaction believed to be mediated to some extent by an antigen-IgE antibody interaction. The symptoms are produced by vasoactive substances, mainly histamine released from mast cells. In contrast, most individuals exhibiting NICU do not have previous sensitization to the substance, and specific antibodies against the causative agent are not found in serum. The mechanism of the NICU reaction is not known, but a direct influence on dermal vessel walls and a non-antibody-mediated release of vasoactive substances (e.g., histamine, prostaglandins, leukotrienes, substance P) have been suggested (Lahti and Maibach, 1985b; 1985c; Lahti *et al.*, 1986; 1987).

3.3.2.1 Human studies

The ability of diethyl fumarate to cause NICU was tested in seven volunteers (Lahti and Maibach, 1985a). Thirty-five microliters of 0.5, 2.0, 10, or 50 mM diethyl fumarate in absolute ethyl alcohol were applied to a 2 x 2 cm area of skin on the upper backs of three females and four males, age 25 to 45 years. Corresponding doses were 0.75, 3.0, 15, and 75 $\mu g/cm^2$, respectively. Absolute ethyl alcohol was applied as a negative control. Responses of the uncovered skin (using visual and palpation methods) were recorded at 10- and 15-minute intervals during the first and second hour, respectively, after diethyl fumarate application. The strength of the NICU reaction was categorized as follows: no reaction, slight erythema, erythema, or erythema with edema.

A dose-related response was observed within 10 minutes, with the maximum NICU appearing at 20 minutes. Absolute ethyl alcohol did not produce a reaction. Slight erythema was observed in two of seven volunteers exposed to 0.5 mM diethyl fumarate, whereas erythema with edema was observed in all seven subjects exposed to 50 mM diethyl fumarate. The NICU disappeared within 75 minutes in all seven subjects at all concentrations. The lowest dose, 0.75 $\mu g/cm^2$, was considered to be the no-observed-adverse-effect level (NOAEL).

In another study, Lahti *et al.* (1987) examined the effect of acetylsalicylic acid (ASA) on the production of NICU. On the first day, 10 µl of 0, 0.5, 2.0, 10, or 50 mM diethyl fumarate in absolute ethyl alcohol were applied using an open (uncovered) application method to a 1 x 1 cm area of skin on the right upper back of 21 test subjects (seven females, 14 males, mean age 39.5 years). These concentrations corresponded to dose levels of 0, 0.86, 3.44, 17.2, and 86 $\mu g/cm^2$, respectively. The test sites were observed for the presence of erythema (-, none to slight; +, moderate to intense) and edema (-, none to slight; +, moderate to intense) every 10 minutes the first hour and every 15 minutes the second hour after administration of diethyl fumarate. Additionally, cutaneous blood flow was measured using non-invasive, laser-Doppler flowometry in eight of the subjects at the skin sites with 50 mM diethyl fumarate. On the following day, the 21 subjects were administered 1,000 mg of ASA orally five hours and one hour prior to repeating the applications of diethyl fumarate as described above, but on the left upper back. Erythema, edema, and cutaneous blood flow were recorded as described above.

A concentration of 10 mM (17.2 $\mu g/cm^2$) diethyl fumarate caused an increase in erythema (13 of 21 subjects) and edema (10 of 21 subjects) compared to the control. In contrast, only 1 of 21 showed a positive reaction for erythema and edema at 2 mM (3.44 $\mu g/cm^2$). Therefore, 3.44 $\mu g/cm^2$ was considered to be the NOAEL in this study. Treatment with ASA produced a significant decrease in the number of positive NICU reactions observed with 10 and 50 mM diethyl fumarate. At the 50 mM test site, it also blocked any increase in cutaneous blood flow that usually follows exposure to a NICU agent. Although the mechanism by which ASA inhibited NICU could not be determined from the experimental design, the authors suggested that it may be due to inhibition of prostaglandin formation (Lahti *et al.*, 1987).

White and Cronin (1984) reported a case of erythema in a 20-year old woman apparently from contact with diethyl fumarate. The woman had been synthesizing the compound in a chemistry laboratory when she developed an itchy, blotchy erythema (without edema) on the back of her hands and on her face about one hour after the start of the synthesis. The reaction disappeared in 24 hours. Patch testing with the organic chemicals she had used in the synthesis gave a positive reaction (red-colored erythema) at the site for diethyl fumarate. The erythema took 10 minutes to develop, but disappeared over the course of the day. The authors suggested that the initial case of erythema the woman experienced may have been due to contact with the diethyl fumarate vapors.

3.3.2.2 Animal studies

Exposure of laboratory animals to diethyl fumarate produced an NICU response similar to that observed in humans. Earlobe swelling was measured in guinea pigs exposed to 0.5, 2.0, 10, or 50 mM of diethyl fumarate in absolute ethyl alcohol (Lahti and Maibach, 1985a). Fifty microliters of the test solutions were applied to both sides of one earlobe of Hartley strain guinea pigs, and absolute ethyl alcohol was applied to the other earlobe as a negative control. The diethyl fumarate doses (in $\mu g/cm^2$) administered to the animals could not be estimated because the surface area of the application site (guinea pig earlobe) was not provided. The inflammatory response was measured by recording the difference in ear thickness measured with a micrometer before application of the diethyl fumarate solutions and at various time intervals for three hours after application.

Diethyl fumarate caused a dose-dependent swelling in the guinea pig earlobe, which was maximal at 30 minutes and gradually decreased over several hours. Absolute ethyl alcohol did not produce a response. The lowest-observed-effect level (LOEL) was 2.0 mM. The dose-response relationship and the response time observed with guinea pig skin was similar to that observed in human skin (Lahti and Maibach, 1985a), except that the swelling persisted longer in the guinea pig ears. The difference in response could be due to more accurate measurement of edema in guinea pigs using the micrometer versus visual and palpation methods in humans. Additionally, guinea pigs were tested in the earlobe whereas humans were tested on the back, and the sensitivity may vary between these two skin sites.

Lahti and Maibach (1985b) compared the responses of guinea pigs, rats and mice to several human NICU agents, including diethyl fumarate. Preparations of test substances in absolute ethyl alcohol (i.e., 1.0% diethyl fumarate, 20% benzoic acid, 10% sorbic acid, 15% cinnamic acid, 20% cinnamic aldehyde, 0.2% methyl nicotinate, or 100% dimethyl sulfoxide) were applied to both sides of one earlobe, while absolute ethyl alcohol was applied to the opposite ear as a control. Although neither the skin surface area nor the actual doses of the test substances were given, the authors stated that the doses applied to the rat and mouse ears were at least the same ($\mu l/cm^2$) as for the guinea pig (guinea pig, 50 µl/ear; rat, 20 µl/ear; mouse, 5 µl/ear). Earlobe thickness were measured before application and at various times for three hours after application of the test substances.

All seven human NICU agents including diethyl fumarate produced erythema and edema in the earlobe of the guinea pig, but only dimethyl sulfoxide and cinnamic aldehyde were reactive in the mouse and rat ear. Absolute ethyl alcohol did not produce a reaction in the three species. Based on the results of this study, it appears that guinea pigs may be the more relevant species for evaluating the potential for NICU reactions in humans.

Lahti and Maibach (1985c) observed that repeated exposures of guinea pig ears to diethyl fumarate elicited a tachyphylactic, or rapidly decreased response, followed by a refractory period. Fifty microliters of 50 mM diethyl fumarate were applied to earlobes and the maximum thickness, which occurred within 60 minutes was measured (day zero). The same ear was treated again on days one, two, four, and eight after the first test. The response (earlobe thickness) as compared to that elicited on day zero, decreased to about 35% of maximum on day one, but slowly increased to 60% on day two, 80% on day four, and 120% on day eight. The authors speculated that the tachyphylaxis observed could be due to slow re-synthesis of the mediators involved, receptor dysfunction in target cells, or decreased reactivity of blood vessels. The decreased response could result in false negative skin tests if the skin test is performed during this refractory period.

3.3.3 Mechanism of Action

The mechanism by which diethyl fumarate elicits the NICU response in humans or laboratory animals has not been elucidated. Several pharmacological substances have been tested in guinea pigs that manipulate the biosynthesis, release, or action of endogenous mediators of the inflammatory response. These include chlorpheniramine and ranitidine, both histamine receptor antagonists; dexamethasone, a steroidal anti-inflammatory agent that inhibits the production of prostaglandins and leukotrienes; indomethacin, a non-steroidal anti-inflammatory agent that inhibits prostaglandin synthesis; and capsaicin, an ingredient in hot peppers which depletes substance P from sensory neurons, resulting in prolonged insensitivity to certain chemical stimuli (Lahti *et al.*, 1986; Gilman *et al.*, 1990).

Pretreatment of guinea pigs with chlorpheniramine and ranitidine had no effect on earlobe swelling from subsequent diethyl fumarate exposure, but it did significantly inhibit the inflammatory reaction induced by a subsequent intradermal injection of histamine. Also, there was no evidence of mast cell degranulation upon histological examination of earlobe tissue. This indicates that endogenous histamine release is probably not a major factor in the production of NICU from diethyl fumarate exposure.

Ear swelling from diethyl fumarate also was not reduced in guinea pigs pretreated with indomethacin, dexamethasone, or capsaicin. This leads one to question the theory that the endogenous release of prostaglandins, leukotrienes, and/or substance P are responsible for diethyl fumarate-induced NICU. It is feasible that other pharmacological agents with similar mechanisms of action may have more of an inhibitory effect on the NICU reaction from diethyl

fumarate, or that some other chemical mediator or a combination of several are responsible for the toxicity of diethyl fumarate in guinea pigs. As mentioned previously, ASA had some inhibitory response on diethyl fumarate-induced NICU in humans (Lahti *et al.*, 1987). However, ASA does not appear to have been tested in laboratory animals, so a direct comparison is not possible. Nevertheless, the physiological responses to diethyl fumarate exposure may be similar in humans and guinea pigs, yet the mechanism of action may be different.

3.3.4 Derivation of Acute Reference Exposure Level

An acute reference exposure level (REL) is derived from the NOAEL, applying an uncertainty factor to compensate for limitations in the data. For dermal exposure to diethyl fumarate, the NOAEL is 0.75 $\mu g/cm^2$, based on an adequately-performed human study (Lahti *et al.*, 1987). To account for differences in sensitivity in the human population, an uncertainty factor of 10 is applied to the NOAEL. The REL, therefore, is 0.75 $\mu g/cm^2/10 = 0.075\ \mu g/cm^2$ or 0.08 $\mu g/cm^2$, or:

$$REL = 80\ ng/cm^2$$

3.3.5 Summary and Conclusions

Examination of the existing toxicological studies for diethyl fumarate indicate that the compound is capable of producing NICU after dermal exposure of both humans and guinea pigs. A dose-related response was evident in both species, and the signs or symptoms of toxicity were similar. In humans, the NOAEL is 0.75 $\mu g/cm^2$, which is the lowest dose reported. The REL calculated from the NOAEL is 0.08 $\mu g/cm^2$.

The mechanism by which diethyl fumarate produces NICU has not been elucidated in humans or laboratory animals. Pretreatment with acetylsalicylic acid (aspirin) inhibits the reaction in humans, which suggests that the human response could be mediated via endogenous prostaglandin release.

4.0 Exposure Assessment

Exposure is a generic term that refers to any type of contact a chemical may have with a living organism that allows for absorption of the substance. For this risk assessment, the "living organism" refers exclusively to humans. Exposure typically occurs via three routes: ingestion, dermal (skin) contact and inhalation, all of which are evaluated in this risk assessment. The amount of chemical presented to the organism for absorption and the amount of chemical actually absorbed are two different "doses." External dose refers to the amount of substance presented to the body for absorption via the three routes mentioned above. The absorbed dose is the amount of the external dose that actually enters the organism or body. In this risk assessment, for the inhalation and ingestion routes, the external and absorbed doses are assumed to be equal. For the dermal route, no specific values for absorption are available for any coproduct, so dermal absorption efficiencies for malathion as detailed in Maibach *et al.* (1971) and used in the *1991 HRA*, weighted proportionately per anatomical site, are used in this risk assessment.

This exposure assessment considers only two scenarios and in that sense is relatively limited, particularly if compared with the *1991 HRA*. In the latter document, numerous scenarios were evaluated that represented a wide range of activities associated with individuals in the malathion-bait-treatment area. The two scenarios evaluated in the current risk assessment are selected from the "upper range" of those evaluated in the *1991 HRA*. The adult and child scenarios selected for evaluation in the current risk assessment are the scenarios that defined the upper boundary of estimated theoretical exposures in the *1991 HRA*: they had the two highest estimated doses out of the range of doses generated for the various scenarios evaluated at that time.

Estimating exposure necessarily involves numerous assumptions and generalizations, all of which contribute to a high degree of uncertainty associated with the estimated dose. For the purposes of this risk assessment, when data are unavailable or judged to be inadequate, assumptions are made with the intent to maximize exposure estimates. For example, when calculating exposure point concentrations of coproducts in environmental media (Section 4.2), the assumption that no volatilization or breakdown of the coproduct occurs during the 24-hour exposure period is likely to overestimate coproduct concentrations in the particular media. The use of the 98^{th} percentile of the deposition data as a basis for calculating exposure point concentrations (Section 4.1.1) is another example of an assumption made to maximize the doses estimated in this risk assessment.

Because of these health-conservative assumptions, it is likely that for virtually all other plausible exposure scenarios, actual doses would be less than those estimated in this risk assessment for these two "high dose" scenarios. Therefore, if risks from exposure to these estimated doses are predicted to be insignificant, then risks to individuals living in the malathion-bait-treatment area would also be insignificant as their exposures to malathion-bait and its coproducts would likely be less. If the risks from exposure to coproducts at these "maximized" theoretical doses are shown to be significant, the risk assessment process would need to be repeated in such a manner

as to more accurately estimate human doses. Where appropriate and if known, specific areas of uncertainty in the exposure assessment are identified. Additionally, Section 6 of this document recommends specific actions to be taken and studies to be performed in order to refine the exposure estimation, thereby reducing the uncertainty in the risk estimates.

This exposure assessment is based on the results of the environmental monitoring performed prior to, during and after the application of a malathion-bait mixture over Garden Grove in May, 1990. As noted previously, current exotic fruit fly eradication programs utilize a malathion-bait mixture containing half the concentration of malathion that was used in the 1989-90 Medfly eradication program in the Los Angeles basin. Experimental design, sampling strategies and actual sample collection was performed by DHS (Brown *et al.*, 1993). Sample analysis was performed by staff of the Hazardous Materials Laboratory of Cal/EPA, then part of DHS. Exposure assumptions and scenarios used in this report are identical to those used in the *1991 HRA* prepared by OEHHA of Cal/EPA, then part of DHS (DHS, 1991a). Although the assumptions made in this document are accompanied by a brief explanation and/or justification, the reader is referred to Section 7: Exposure Estimation in the *1991 HRA* for a more detailed discussion.

4.1 Environmental Sampling Results

In order to maximize the proportion of the population considered in this risk assessment, all concentrations in environmental media are given as the mean concentration and the 98th percentile concentration, the latter calculated as: [mean+3SD]. Doses are estimated for the scenarios and special cases using both the mean and the 98th percentile environmental concentrations. All monitoring data used in this risk assessment were obtained from the following sources:

> Brown, M.A., Petreas, M.X., Okamoto, H.S., Mishke, T.M., and R.D. Stephens. "Monitoring of Malathion and Its Impurities and Environmental Transformation Products on Surfaces and in Air Following an Aerial Application," *Environmental Science and Technology*, Volume 27 (2), pp. 388-397, 1993, (Brown *et al.* 1993).
>
> "Pilot Study for the Environmental Monitoring of Malathion, Malathion Impurities and Their Environmental Transformation Products on Surfaces and in Air During and After an Aerial Application in Garden Grove, California in May of 1990," by the same authors, Department of Health Services, December 1991, (DHS 1991b).

Details of the actual sampling protocol and analytical methodology that generated the data which served as a basis for the estimated doses, and thus the risk estimates presented in this document, are found in Brown *et al.*, 1993. Three data sets are used from the publications for this risk assessment. These include the analytical results from tank mix samples, malathion-bait

deposition cards (Kimby cards), and from air samples. Each data set is used, without correction for recovery, as follows:

> Deposition data. The bulk of the exposure calculations are based on this data set. Deposition onto three different surface types was monitored for malathion, malaoxon and for five coproducts, including the three selected for evaluation. For the purposes of consistency between this risk assessment and the *1991 HRA*, deposition onto Kimby cards is utilized for the calculation of mean and 98th percentile of exposure point concentrations in water, soil, and homegrown produce. Exposure point concentrations along with the deposition data are used for the estimation of human doses via the oral and dermal routes. Data reflecting deposition onto Teflon surfaces and onto filter paper are not used for this risk assessment.
>
> Air monitoring data. Outdoor air monitoring data are used to calculate the mean and 98th percentile outdoor and indoor air concentrations, from which human inhalation doses are estimated. These data are available for OOS(O) and diethyl fumarate, but not for isomalathion. Air monitoring data for malaoxon are used as a surrogate for isomalathion.
>
> Tank mixture data. These data are used to help determine the suitability of malaoxon as an appropriate surrogate for isomalathion. (Note: It is these data that are used for the verification of the isomalathion concentration, which should not be greater than 1.8% of the nominal malathion concentration; see WHO, 1978.)

4.1.1 Mass Deposition

Because of its more comprehensive nature, the appendix to the DHS publication (DHS, 1991b) serves as the source of the deposition data used in this risk assessment. As previously mentioned, for purposes of consistency with the *1991 HRA*, only deposition onto Kimby cards is considered in preparing this risk assessment, which also was the deposition surface used in the prior document. Analytical values are utilized as they appeared in the appendix; no correction for recovery is performed. (Note: Recoveries of coproducts from deposition surfaces ranged between 60 to 90%, therefore, the analytical results presented in Table 4-1 represent minimum values.) The vast majority of deposition (>95%) occurred "during" the application (using approximately one hour as the "deposition time"). Therefore, for deposition-dependent calculations, the mean deposition and the 98th percentile [mean+3SD] of the deposition data are calculated solely from the "during" data. Deposition monitoring was conducted in duplicate at three separate locations. The analytical results from all three collection locations are pooled, from which the arithmetic mean and standard deviation are calculated. When the deposition values are less than the limit of detection, the limit of detection is substituted, rather than one-half the limit of detection as is commonly, but arbitrarily, done. This assumption does not have a significant impact on the results as only two data points for one coproduct [OOS(O)] are below

the detection limit. All values are reported in the publication as μg/ft^2 and were converted to μg/m^2 before use. Table 4-1 shows the individual analytical results of the mass deposition of "indicator coproducts" onto Kimby cards "during" the application of a malathion-bait mixture.

4.1.2 Air

The scenarios evaluated in this risk assessment assume a 24-hour exposure period. The outdoor air concentration of coproduct during that period is estimated as a time-weighted average of the outdoor air coproduct concentration "during" the application (one hour) and the outdoor air concentration post application (23 hours) and is calculated as follows:

C_o = $[C_d(1) + C_p(23)]$ / 24 hours

where:

C_o = outdoor air coproduct concentration over the 24 hour exposure period,

C_d = outdoor air coproduct concentration during malathion-bait application, and

C_p = outdoor air coproduct concentration post malathion-bait application.

Mean outdoor air concentrations are calculated from the average outdoor air coproduct concentration during an application and the average outdoor air coproduct concentration post application. The 98th percentile concentration is calculated in an analogous manner by substituting the [mean+3SD] in place of the mean. As described in the *1991 HRA*, indoor air concentrations of malathion and malaoxon were found to be significantly lower than those found outdoors. For malaoxon, indoor air concentrations were only, on average, 12% of the outdoor malaoxon air concentrations (see *1991 HRA*, Table 7-8, page 7-24). Accordingly, for the purposes of inhalation dose estimation in this risk assessment, indoor air concentrations are adjusted to 12% of those measured outdoors.

As mentioned, air monitoring data are available for only two of the three indicator coproducts; diethyl fumarate and OOS(O). For diethyl fumarate, however, exposure point concentrations in air are not calculated, as the local effects due to a topical dose are the only effects under consideration. Presently, any contribution from volatilized material in the air to a surface or topical dose is not calculable.

Because no monitoring data are available for isomalathion, air concentrations of this coproduct are approximated by the use of a surrogate, malaoxon. Based on their chemical structures, the assumption is made that the vapor pressures of these two coproducts (isomalathion and malaoxon) are within an order of magnitude of each other. Coproducts are present in air as the result of their volatilization from two sources: malathion-bait as it drops to the ground and bait that has already deposited onto the ground. Accordingly, the relative air concentrations of isomalathion and malaoxon would be expected to approximate their ratios measured in the tank

mix and in the deposition samples taken during the application. Review of the analytical results for the 16 individual tank mixes in use during the study reveals an average isomalathion/malaoxon ratio of approximately 1.5 with very little analytical variability [standard errors are: 0 for OOO(S) and OOS(O), 0.001 for malaoxon, 0.002 for isomalathion, and +/- 0.003 for diethyl fumarate and OOS(S)]. The isomalathion/malaoxon ratio for deposited material is essentially reversed: 0.6. Since these ratios approximate one, outdoor air concentrations of malaoxon are used without correction as surrogates for outdoor air concentrations of isomalathion. We recognize that due to differences in the mechanisms of formation, the amount of malaoxon available for volatilization increases over time following a malathion application, while the amount of isomalathion probably does not. Accordingly, only malaoxon outdoor air concentrations measured "during" the application (one hour) are used and are not time-weighted with outdoor air concentrations measured post application. The measured outdoor air concentrations of OOS(O) and "isomalathion" (malaoxon) along with their calculated mean and 98^{th} percentile exposure point concentrations are provided in Table 4-2, as are the calculated indoor air concentrations.

4.2 Estimated Concentrations in Environmental Media

Direct measurements of coproduct concentrations were made for air, tank mixes and mass deposition surfaces. No analytical measurements are available for soil, for homegrown vegetables, or for water (wading and swimming pools). Accordingly, coproduct concentrations in these media are estimated using the mass deposition results.

4.2.1 Soil

Consistent with the *1991 HRA*, the mean and 98th percentile soil concentrations of isomalathion and OOS(O) in soil are calculated for two different mixing depths; 1.0 cm (for a child with pica) and 0.1 cm (all other applications). For the case of a child with pica, it is assumed that they would consume a "scoop" of soil, rather than simply scratch the surface, hence a 1.0 cm mixing depth is used in the calculations. All other scenarios assume essentially no mixing (0.1 cm) over the short (24-hour) time period under evaluation. The soil density is assumed to be 1.5 grams/cm^3 (as it was in the *1991 HRA*), a density typical of urban soils (Brady, 1984).

No information is available regarding the environmental behavior of the indicator coproducts. Therefore, in order to maximize exposure estimates, it is assumed that no degradation or volatilization of the deposited material occurred during the 24-hour exposure period. In other words, we assume that all coproduct that deposited on the soil surface remained and would be available for contact and/or consumption during the hypothetical 24-hour exposure period

Table 4-1. Selected results[a,b] of coproduct mass deposition monitoring during[c] malathion-bait application.

Deposition of Coproduct (μg/ft^2) on Kimby cards.			
Location	Isomalathion	Diethyl Fumarate	OOS(O)
site A	1.5, 0.92	5.0, 10.0	0.60, 0.44
site B	1.3, 1.3	14, 15	<0.71, <0.71
site C	3.7, 5.7	6.6, 4.9	0.08, 0.10
mean	2.4	9.3	0.23
SD	1.9	4.5	0.23
98th percentile	8.1	22.8	0.9
in μg/m^2 [d]			
mean	25.8	100.1	2.5
98th percentile	87.2	245.4	9.9

a The deposition surface, Kimby cards were located in duplicate at three locations in the application area. Values shown in the table are the average of duplicate analysis of each card.

b Where the values are less than the limit of detection, the limit of detection is substituted (e.g., OO(S)O, site B).

c During application is defined as the time period from initiation of the application to its conclusion, approximately one hour in length.

d To convert from μg/ft^2 to μg/m^2, multiply by 10.764 ft^2/m^2

considered in this assessment. (For reasons similar to those given above, no calculations are performed for diethyl fumarate.) The coproduct concentration in soil is given by:

$$C_S = [D_S / (V_S \times S_d)] \times (10^3 \text{ ng}/\mu\text{g})$$

where:

C_s = soil concentration of coproduct (ng/grams),
D_s = deposition of coproduct onto soil (μg/m^2),
V_s = soil volume per square meter of surface (cm^3/m^2), and
S_d = soil density (assumed to be 1.5 grams/cm^3).

For a mixing depth of 1 cm:

$$V_{s1} = 1 \text{ m x } 1 \text{ m x } 1 \text{ cm} = 100 \text{ cm x } 100 \text{ cm x } 1 \text{ cm} = 10{,}000 \text{ cm}^3$$

For a mixing depth of 0.1 cm:

$$V_{s0.1} = 1 \text{ m x } 1 \text{ m x } 0.1 \text{ cm} = 100 \text{ cm x } 100 \text{ cm x } 0.1 \text{ cm} = 1{,}000 \text{ cm}^3$$

Mean soil concentrations are calculated using mean deposition values. The 98th percentile concentration is calculated in an analogous manner by using the [mean + 3 SD] in place of the mean. Estimated concentrations of coproducts in soil can be found in Table 4-3.

Table 4-2. Measured and calculated coproduct concentrations in air.

	Airborne Coproduct Concentrations (ng/m^3)[a]			
	During Application (outdoor)	Post Application (outdoor)	Time Weighted Average (outdoor)	Estimated Indoor[b]
OOS(O)				
mean	29.5	2.5	3.6	0.43
98th percentile	48.7	4.9	6.7	0.80
Isomalathion[c]				
mean	5.4	d	5.4	0.65
98th percentile	7.2	d	7.2	0.86

a Mean values are the results of individual analysis from three sites (n=3). The 98th percentiles are calculated as the mean + 3SD.

b Indoor air concentrations are estimated as 12% of those found outdoors. See text for additional discussion.

c Analytical values are those for malaoxon and are being used in this risk assessment as surrogates for air concentrations of isomalathion. See text for additional discussion.

d Post application malaoxon outdoor air concentrations are not used as surrogates for isomalathion outdoor air concentrations. See text for additional details.

Table 4-3. Calculated coproduct concentrations[a] in soil, homegrown produce and pool water.

	Environmental Media				
	Soil[b] (ng/g)		Produce[c] (ng/g)	Pool Water[d] (µg/L)	
	1 cm (pica child)	0.1 cm (all others)	(adult)	4 ft (child)	0.5 ft
OOS(O)					
mean	0.17	1.7	0.43	0.002	0.16
98th percentile	0.67	6.7	1.72	0.008	0.065
Isomalathion					
mean	1.7	17.2	4.5	0.021	0.17
98th percentile	5.8	58.1	15.2	0.071	0.57
Scenario[e,f]	1CS	1A, 1C	1A, 1C	2AS	3CS

a Values are calculated from the "during" deposition data which are shown in Table 4-1.

b Specifics of the calculations for coproduct concentrations in soil are found in Section 4.2.1.

c Specifics of the calculations for coproduct concentrations in homegrown produce are found in Section 4.2.2.

d Specifics of the calculations for coproduct concentrations in pool water are found in Section 4.2.3.

e The scenario or special case in which a particular exposure point or environmental medium coproduct concentration is used in the estimation of dose. Abbreviations are: 1A = #1Adult; 2AS = #2A Special; 1C = #1Child; 1CS = #1C Special; 3CS = #3C Special. Refer to Section 4.3, Estimation of Pathway-Specific Exposure, for a detailed discussion of the scenarios and special cases.

f Note: #1A Special, #2C Special and #4C Special are situations involving malathion-bait as the exposure medium and as a result, are not included in this table. "Exposure point" concentrations are, for all practical purposes, the mass deposition values which are shown in Table 4-1.

4.2.2 Homegrown Produce

No data are available that characterize the environmental fate of malathion coproducts on garden vegetables. Therefore, for homegrown produce, it is assumed that all malathion-bait deposited on the crop adhered, that no degradation or volatilization of the deposited material occurred during the 24-hour exposure period, and that contaminated produce is not washed before consumption. The net result of these assumptions is that all malathion-bait deposited on the surface of the crops is considered available for absorption. These assumptions, which are consistent with those made in the *1991 HRA*, would likely overestimate exposures. Based on CDFA data regarding the production of lettuce and broccoli in California for the years 1986-87, an average yield of 2.3 kg/m^2 (CDFA 1986, 1987) is assumed from crops whose harvested portion covered 40% of the soil surface (Baes *et al.*, 1984).

The coproduct concentration in homegrown produce is given by:

$$C_p = [(D_p \times I_f) / Y_c] \times 10^3 \text{ ng/µg} \times 10^{-3} \text{ kg/grams}$$

where:

C_p = concentration of coproduct in homegrown produce (ng/grams),
D_p = deposition of coproduct onto produce ($\mu g/m^2$),
I_f = interception fraction (0.40), and
Y_c = crop yield (2.3 kg/m^2).

Mean coproduct concentrations are calculated using mean deposition values. The 98th percentile concentration is calculated similarly, by substituting the [mean+3SD] in place of the mean. Calculated coproduct concentrations in homegrown produce are found in Table 4-3.

4.2.3 Water

The concentration of coproduct in a six inch deep wading pool is estimated using deposition data, and is used for exposure scenarios involving children, as was the case in the *1991 HRA*. For adult exposure scenarios, concentrations are estimated similarly, however, an average water depth of four feet instead of six inches (swimming pool versus wading pool) is assumed. No information is available regarding the environmental behavior of malathion coproducts in water. Therefore, it is assumed that no degradation or volatilization of the deposited material occurred during the 24-hour exposure period. A uniform distribution of coproducts in the water is also assumed.

The coproduct concentration in pool water is given by:

$$C_w = (D_w \times S_a) / V_p$$

where:

C_w = concentration of coproduct in body of water (µg/L),
D_w = deposition of coproduct onto surface of water (µg/m^2),
S_a = surface area of body of water (m^2), and
V_p = volume of body of water (L)

For ease of calculations, a surface area of one square meter is used in the calculations. Note that the calculated coproduct concentration is constant, regardless of surface area, at a constant depth. The volume of water in a six inch-deep wading pool with a surface area of one square meter is given by:

$V_{p0.5}$ = 100 cm x 100 cm x (0.5 ft)(0.305 m/ft)(100 cm/m)
= 152,000 cm^3
= 152 L

For a swimming pool with an average depth of four feet, the volume is:

V_{p4} = $V_{p0.5}$ x (4 feet/0.5 feet)
= $V_{p0.5}$ x 8
= 1,216 L

Mean coproduct concentrations in swimming and/or wading pools are calculated using mean deposition data. The 98th percentile concentration is calculated by substituting the [mean+3SD] in place of the mean. Estimated concentrations of coproducts in swimming and wading pools are shown in Table 4-3.

4.2.4 Summary of Exposure Point Assumptions

Air. Outdoor concentrations of OOS(O) are calculated from monitoring data as a time-weighted average of the airborne coproduct concentrations during the application (one-hour "weight") and those monitored post application (23-hour "weight"). Outdoor air concentrations of isomalathion are approximated in this risk assessment by the use of a surrogate, malaoxon. "Isomalathion" outdoor air concentrations are not time-weighted, but are based on outdoor one-hour air concentrations of malaoxon measured during an application. Based on data from the *1991* HRA, it is assumed that indoor air concentrations of coproducts are approximately 12% of the concentrations found outdoors.

Soil. Homogeneous mixing is assumed (0.1 cm depth for all except child with pica, in which case the mixing depth is assumed to be 1.0 cm). It is also assumed that there would be no degradation or dissipation of coproducts during the exposure period. A soil density of 1.5 grams/cm^3 is used in the calculations.

Produce. It is assumed that all malathion-bait deposited on leafy vegetables grown outdoors adhered to the surface and that the residues did not breakdown or wash off during preparation. It is also assumed that 40% of the soil surface is covered with the edible portion of a crop with an average yield of 2.3 kg/m^2.

Water (swimming). For both the adult and child, water concentrations are estimated from deposition data. For exposures involving children, a wading pool with an average depth of six inches is assumed. For the adult, concentrations are estimated similarly, except that an average depth of four feet is used in the calculations. It is assumed that there would be no dissipation or breakdown of coproduct during the exposure period.

The specific values selected for the various parameters are referenced in the text. Please consult Section 4.1.2 for air, 4.2.1 for soil, 4.2.2 for homegrown produce, and 4.2.3 for pool water.

4.3 Estimation of Pathway-Specific Exposure

Exposure pathways evaluated in this risk assessment are identical to those found in the *1991 HRA* and include: inhalation (ambient air), ingestion (soil; homegrown produce; malathion-bait), and dermal (transfer from contaminated surfaces; swimming in contaminated water; direct deposition of malathion-bait on skin). Figure 4-1 shows the exposure pathways evaluated in this risk assessment and the relationship between human activities and contact with contaminated environmental media.

The *1991 HRA* served as a guide for the selection of scenarios leading to the greatest exposure, also known as "worst case." As previously mentioned, not only do the behaviors defining the scenarios result in maximum exposure, but the individual parameters (shown in Table 4-4) that define the behaviors are selected in order to maximize the estimated doses. Accordingly, worst-case exposure to "the representative adult and child" are evaluated as are six "special cases" (two for adults and four for children).

The potential for subchronic exposure to malathion coproducts is relatively high, with possible exposure from all three routes. Repeated applications of malathion-bait and/or repeated contact with contaminated media would lead to exposures over a period of days to possibly weeks or even months. Two major limitations of the data base preclude any realistic evaluation of the risk from subchronic and/or chronic exposure to the coproducts. First; no toxicology data are available regarding the effects of repeated exposures to these chemicals. Secondly, no environmental fate data are available for any coproduct. Uncertainties already present in this assessment plus additional uncertainties contributed by new assumptions (e.g., environmental half-life) would render any resulting chronic and/or subchronic risk estimate unreliable. Therefore, due to analytical and toxicological data limitations, only acute exposure scenarios are evaluated in this risk assessment of exposure to selected malathion coproducts.

EXPOSURE PATHWAY	ENVIRONMENTAL EXPOSURE POINT[a]	HUMAN ACTIVITY ASSOCIATED WITH EXPOSURE POINT "CONTACT"
Inhalation	Air	breathing contaminated air
Ingestion	Soil	hand to mouth behavior; pica (children)
	Produce	eating homegrown produce
	Water	accidental ingestion while swimming
Dermal Contact	Outdoor surfaces	direct contact with contaminated surfaces
	Soil	direct contact with contaminated soil
	Water	swimming in contaminated water
	Air	contact with falling particles

a also known as environmental media or contaminated environmental media

Figure 4-1. Human exposure pathways.

For the purposes of this risk assessment, the populations exposed to the malathion coproducts are represented by the following:

Adults. The representative of this age group is a very active 70 kg outdoor worker, who spends 12 hours/day outside (eight hours of work and four hours for personal activities wearing shorts only), 12 hours per day inside resting, and eats exclusively home-grown fruits and vegetables This hypothetical receptor is identified in the risk assessment as: #1 Adult. Exposure is also estimated, separately, for an adult in the following two "special case" situations:

1) an adult who is outside during malathion-bait application and receives a dermal dose of "bait" directly on their exposed skin (#1A Special); and/or

2) an individual who, on the day of application, swims for an hour in a pool (average depth of four feet) contaminated by coproducts (#2A Special).

Children. This age group is represented by a very active two year old weighing 13.4 kg who spends an average of eight hours per day playing "actively" outside (shorts only) and spends 16 hours per day resting indoors. It is assumed, as it is in the *1991 HRA*, that this child wears only shorts while playing outdoors. In addition, this child eats exclusively homegrown vegetables. This hypothetical receptor is identified in the risk assessment as: #1 Child. Estimated separately is the exposure for a child under four different sets of special circumstances: Specifically evaluated is the dose received by a child who:

1) exhibits pica behavior (#1C Special); and/or
2) is outside during malathion-bait application (#2C Special); and/or
3) "swims" for one hour in a contaminated wading pool (6 inch depth) on the day of application (#3C Special); and/or
4) twice daily, consumes malathion-bait that has become stuck to their hands (265 cm^2 area) from touching contaminated outdoor surfaces (#4C Special).

Assumptions used for the estimation of dose are the same as those used for the analogous scenario in the *1991 HRA*, are described in the text and can be seen in Table 4-4. Additional discussion is found in the *1991 HRA*, Section 7; Exposure Estimation.

4.3.1 Inhalation

With the exception of special cases, the highest estimated inhalation doses estimated in the *1991 HRA* were those for the very active individual, either child or adult. Accordingly, those are the health protective inhalation scenarios selected for evaluation in this risk assessment. As discussed earlier in this document, outdoor air concentrations of coproducts are used for the outdoor component of the inhalation dose and are adjusted for use as indoor air concentrations. The inhalation component of coproduct dose is calculated as follows:

$D_{inhalation} = (V_oC_o + V_iC_i)/ BW$

where:

$D_{inhalation}$ = dose received by the inhalation route (ng/kg-day),
V_o = volume of outdoor air inhaled per day (m^3/day),
C_o = concentration of coproduct in outdoor air (ng/m^3),
V_i = volume of indoor air inhaled per day (m^3/day),
C_i = concentration of coproduct in indoor air (ng/m^3), and
BW = body weight (kg).

Table 4-4. Assumptions[a] used in dose estimation calculations.

Parameter (units)	Adult	Child	Text Symbol[b]
volume of indoor air inhaled/day (m^3/day)	10	2	V_i
volume of outdoor air inhaled/day (m^3/day)	15	5	V_o
fruit and vegetables consumed/day (grams/day)	231	108	P_c
soil consumed/day (grams/day)	0.1	0.33 (ave)	S_c
		10 (pica)	S_c
surface area of both hands (cm^2)	n/a	265	n/a
transfer coefficient (cm^2/hour)	3,500	1,050	T_c
absorption efficiency (legs,arms,hands)[c] (unitless)	0.082	0.093	A_d
absorption efficiency (torso,arms,legs,hands,feet,face)[c] (unitless)	0.093	0.093	A_d
surface area (entire body) (cm^2)	18,000	6,000	S_b
surface area (legs,arms,hands) (cm^2)	10,290	3,340	S_s
skin permeability constant (L/cm^2-hour)	0.001	0.001	K_p
body weight (kg)	70	13.4	BW

n/a not applicable

a Assumptions in this HRA are the same as those made in the *1991 HRA* for the analogous scenario. Justification and references for the various assumptions are given in the text of this document. A more detailed discussion of the selection of these assumptions is found in the *1991 HRA*, Section 7, Exposure Estimation.

b Symbol used in the text of this document (equations) for the particular parameter.

c A "surface-area weighted average" of the anatomic region-specific malathion absorption factors; see *1991 HRA*, pages 7-52 through 7-55 for greater detail.

Assumptions of "respiratory volumes" for the adult and child used in this calculation are provided in Table 4-4 and are based on the mid-range of the normal distribution of breathing rates for the specific age group (U.S. EPA, 1985). This scenario assumes that for the adult 16 hours per day are spent "resting" with a corresponding ventilation rate of approximately 10 liters per minute and eight hours per day are considered "active" with a ventilation rate of approximately 30 liters per minute. Children in this scenario spend 12 hours per day at rest and an equal amount of time "active," with ventilation rates of approximately 4.7 and 6.6 liters per minute, respectively. These assumptions are the same as those for $Case_{inh}2$ adult "outdoor worker" and $Case_{inh}5$ "very active child" as shown in Table 7-16, page 7-39 of the *1991 HRA*. Concentrations of coproducts in outdoor air are based on actual levels monitored subsequent to a malathion-bait application. Indoor air concentrations are estimated as 12% of those found outdoors based on information presented in the *1991 HRA.* Calculation of exposure point coproduct concentrations in air are shown in Section 4.1.2 of this document. Estimated doses via the inhalation route are provided in Tables 4-5 and 4-7 for the representative adult and child, respectively.

4.3.2 Ingestion

The dose due to oral ingestion is calculated as follows:

$$D_{ingestion} = [(P_c\, C_p) + (S_c\, C_s)] / BW$$

where:

$D_{ingestion}$ = dose by the ingestion route (ng/kg-day),
P_c = amount of produce consumed per day (grams/day),
C_p = coproduct concentration in produce (ng/grams),
S_c = amount of soil consumed per day (grams/day),
C_s = coproduct concentration in soil (ng/grams), and
BW = body weight (kg).

Assumptions used in this calculation are shown in Table 4-4, and are identical with those used for $Case_{ing}4a\&b$ "soil" and "garden vegetables," $Case_{ing}5$ "pica," and $Case_{ing}6$ "surface touching" in the *1991 HRA* (Table 7-17, page 7-42). Soil consumption rates for adults of 100 mg/day and for non-pica children of 330 mg/day are average values as reported in Sedman (1989). A high value of 10 grams/day, intended to represent a serious case of pica, is 30 times higher than the estimated daily rate for a child (U.S. EPA, 1989), is included for the purposes of comparison with the *1991 HRA* (DHS, 1991).

Consumption of home grown produce is based on the 95^{th} percentile of vegetable consumption per eating occasion for the given age group (USDA, 1982). The specific values utilized in the calculations (231 grams/day for the adult; 108 grams/day for the child) are shown in Table 4-4, along with other assumptions made for the purposes of dose estimation.

Direct consumption of malathion-bait is considered in the ingestion scenario, #4C Special. In this special circumstance, malathion-bait transferred from contaminated surfaces to the palm and fingers of a child's hands (265 cm^2 surface area; U.S. EPA 1985) is ingested twice daily. To maximize the dose estimate, it is further assumed that the transfer of the deposited material to the hands is 100%. Therefore, the amount of coproduct consumed per day is:

{2 events/day} x {deposition value ($\mu g/m^2$)} x {surface area of hands (.0265 m^2)}

= µg coproduct ingested/day

Dose levels, based on the coproduct concentrations estimated in Sections 4.2.1 and 4.2.2, for soil (0.1 cm mixing depth) and produce, respectively, are estimated for the ingestion route and are seen in Tables 4-5 and 4-7 for the worst-case representative adult and child, respectively. Estimates, based on soil coproduct concentrations (Section 4.2.1; 1 cm mixing depth) and deposition data (Section 4.1.1), of the ingested dose for the "child" special cases of pica and surface touching are shown in Table 4-8.

4.3.3 Dermal Absorption

Dermal exposure to malathion coproducts can occur by several different processes. Included in this evaluation are three possible dermal exposure pathways: 1) transfer from contaminated surfaces; 2) malathion-bait deposition directly on the skin; and 3) transfer from contaminated "environmental media" (e.g., water). Each process has its own set of considerations and is, therefore, calculated in a manner specific for that variant of the dermal route.

Estimated doses via the dermal route of exposure are shown in Table 4-5 for the representative adult and Table 4-7 for the representative child. Exposure estimated for the special cases of direct deposition onto the skin and dermal absorption from swimming in contaminated water are seen in Tables 4-6 and 4-8 for the adult and child, respectively.

4.3.3.1 Transfer from Contaminated Surfaces:

This pathway is based on physical contact with a contaminated surface. Dose estimates due to the transfer of coproduct from a contaminated surface to the skin are calculated as follows:

$$D_{dc} = Dep_d \, T_c \, D_e \, A_d / BW$$

where:

D_{dc} = dose due to dermal contact (ng/kg-day),
Dep_d = deposition of malathion-bait (ng/cm^2),
T_c = transfer coefficient (cm^2/hr),
D_e = duration of contact with surface (hrs/day),

A_d = absorption efficiency (unitless), and
BW = body weight (kg).

Assumptions made for the purposes of this calculation are provided in Table 4-4 and are the same as those used in the *1991 HRA* for: $Case_{derm}3$, a "very active" adult and $Case_{derm}5$, a "very active" child (Table 7-18, page 7-44 of the *1991 HRA*). In the *1991 HRA*, the daily contact with contaminated outdoor surfaces is assumed to be eight hours for the child and four hours for the adult. For the purposes of consistency, the same "contact periods" are used in this risk assessment. No values for absorption efficiency are available for any of the coproducts under study. For the purposes of these calculations, a surface area weighted average of the anatomically specific absorption efficiencies for malathion (Maibach *et al.*, 1971) is used as a substitute (not surrogate) for the dermal absorption efficiency of both OOS(O) and isomalathion. The transfer coefficients used in this calculation are (T_c) = 3,500 cm^2/hour and 1,050 cm^2/hour for adults and children, respectively (Fong *et al.*, 1990).

The estimated dermal doses from contact with contaminated surfaces, are based on the mean and 98^{th} percentile coproduct deposition values (seen in Table 4-1) and are presented in Tables 4-5 and 4-7 for the representative adult and child, respectively.

4.3.3.1.1 Transfer from Contaminated Surfaces - Special Case

As described earlier, exposure to the coproduct diethyl fumarate can result in skin irritation localized at the point of contact, a condition known clinically as non-immunologic contact urticaria (NICU). Unlike the other coproducts, it is the topical dose that is of concern, rather than the absorbed (or systemic) dose. Specifically, the "surface concentration" (amount of chemical per unit surface area) is the toxicological determinant in the production of NICU. The absorbed or systemic dose is not directly relevant to this particular endpoint.

A somewhat modified approach to dose estimation is necessary for this type of agent. By definition, this is a surface dose and is therefore not absorbed. Therefore, the absorption term in the equation used for estimating dermally absorbed doses due to contact with contaminated surfaces is modified by eliminating the absorption term (Section 4.3.3.1). Furthermore, as the dose is normalized to unit surface area rather than unit weight, the estimated total dose is divided by body surface area, not body weight, as are all other dose estimates. The result is an expression that estimates the "daily" surface concentration of coproduct (ng/cm^2-day) and is as follows:

$D_s = Dep_d \, T_c D_e / S_b$

where:

D_s	=	surface dose (ng/cm^2-day),
Dep_d	=	deposition of malathion-bait (10 ng/cm^2-mean; 25 ng/cm^2-98th percentile),
T_c	=	transfer coefficient (3,500 cm^2/hour for adult; 1,050 cm^2/hour for child),
D_e	=	duration of contact with contaminated surface (8 hours/day, child; 4 hours/day, adult), and
S_b	=	surface area of human body (18,000 cm^2 for adult; 6,000 cm^2 for child).

The assumptions used in these calculations are the same as those discussed in Section 4.3.3.1, "Transfer from Contaminated Surfaces" and are identical with those used for $Case_{derm}$ 3; adult and $Case_{derm}$ 5; child in the *1991 HRA* (Table 7-18, page 7-44 of the *1991 HRA*). The surface dose estimates for diethyl fumarate are shown in Tables 4-5 and 4-7 for adults and children, respectively.

4.3.3.2 Direct Deposition:

A plausible scenario would be that of an individual remaining outside during a malathion-bait application and thereby receiving a coproduct dose directly from the malathion-bait. Accordingly, in this section coproduct doses are calculated from the direct deposition of malathion-bait on the skin, for both the adult and child. The dose received via this variant of the dermal route can be calculated as follows:

$D_{dc} = Dep_d \, E_d S_s A_d / BW$

where:

D_{dc}	=	dose due to dermal contact (ng/kg-day),
Dep_d	=	deposition of malathion-bait (ng/cm^2),
E_d	=	number of "deposition events" per day (1/day),
S_s	=	surface area of exposed skin (cm^2),
A_d	=	absorption efficiency (unitless), and
BW	=	body weight (kg).

For the purposes of this evaluation, it is assumed that the individual would be wearing shorts, shoes and shirt. Therefore, the head, arms, legs, and hands would be the exposed skin surfaces. Again, the absorption efficiency for malathion, in this case averaged across the head, legs, arms, and hands, is used in the calculations as there is no value available for any of the coproducts. Note that this scenario was evaluated in the *1991 HRA* for a 10 year old child rather than a two year old as is done in this risk assessment. Other than this, all assumptions made in this exposure

estimation (shown in Table 4-4), are the same as those made in the *1991 HRA* for $Special_{derm}1$, "direct malathion-bait deposition" - adult and $Special_{derm}3$, "direct malathion-bait deposition" - child (Table 7-18, page 7-44 of the *1991 HRA*).

Estimated doses for the special cases of direct deposition onto the skin are provided in Tables 4-6 and 4-8 for the adult and child, respectively.

4.3.3.3 Dermal Exposure From Contact with Contaminated Water:

The absorption of coproducts from exposure to contaminated water is calculated using the approach taken by Bogen *et al.* (1988) for a residential exposure to contaminated water while showering. Dermal exposure is estimated as follows:

$$D_{dc} = J_s D_e F_s A_s / BW$$

where:

D_{dc}	=	dose due to dermal contact (ng/kg-day),
J_s	=	steady-state flux across skin (ng/cm^2-hour),
D_e	=	duration of contact (hours/day),
F_s	=	fraction of skin surface in contact with water(unitless),
A_s	=	exposed skin surface area (cm^2), and
BW	=	body weight (kg).

Assuming Fick's Law is observed, then:

$$J_s = K_p D_c$$

where:

K_p = Permeability constant. No specific value is available for any coproduct. For the *1991 HRA*, the value of 0.001 L/cm^2, determined for toluene, was used as a health-conservative "estimate" since it was the highest literature value available for any compound. For purposes of consistency with the *1991 HRA*, and because no value for this constant is available for any coproduct, the value used in the *1991 HRA* is also used in these calculations.

D_c = Coproduct concentration difference across the tissue. In effect, this is the water concentration (ng/L) of the coproduct as the coproduct body burden is assumed to be zero prior to exposure.

Assumptions made for this scenario are provided in Table 4-4 and are the same as those used in the *1991 HRA* for: Special$_{derm}$2, "swimming pool" and Special$_{derm}$5, "wading pool" representing adults and children, respectively (Table 7-18, page 7-44 of the *1991 HRA*).

In addition to the dermally absorbed dose from swimming, a small amount of exposure also occurs while swimming due to the inadvertent swallowing of pool water. As in the *1991 HRA*, the amount of water swallowed is assumed to be 0.1 L. The amount of coproduct contained in this volume divided by body weight [(0.1 L)(ng/L)/BW] has been added to the doses calculated for dermal exposure to contaminated water and are included in the dose estimates for this scenario. Dose estimates due to swimming in contaminated water are shown in Tables 4-6 (adult) and 4-8 (child).

Table 4-5. Estimated doses[a] for the "representative adult" (ng/kg-day or ng/cm^2-day).

	Inhalation	Ingestion		Dermal
		soil	vegetables	surface transfer
Isomalathion:				
Mean:	1.3	0.02	14.8	48
98th percentile:	1.7	0.08	50.2	162
OOS(O):				
Mean:	0.8	0.002	1.4	4.7
98th percentile:	1.6	0.010	5.7	18.4
Diethyl Fumarate:				
Mean:	b	b	b	7.8[c]
98th percentile:				19.4[c]

a Doses are estimated using both the mean and the 98th percentile environmental concentrations. Estimates of dose based on mean environmental concentrations are identified in the table as "Mean." Estimates based on the 98th percentile environmental concentrations are identified as "98th percentile."

b Because of the nature of the toxic endpoint evaluated for diethyl fumarate (NICU), the calculation of doses via the inhalation and ingestion routes is unnecessary.

c Dosage units for diethyl fumarate are ng/cm^2-day; a surface concentration. See section 4.3.3.1.1, "Transfer from Contaminated Surfaces: Special Case" for more details.

Table 4-6. Estimated dermal doses[a] for an adult from direct malathion-bait deposition on the skin and swimming in contaminated water (ng/kg-day).
(Special cases #1A and #2A, respectively)

	Direct Deposition	Swimming
Isomalathion:		
Mean:	31	5.4
98th percentile:	105	18.0
OOS(O):		
Mean:	3.0	0.5
98th percentile:	11.9	2.0

a Doses are estimated using both the mean and the 98th percentile environmental concentrations. Estimates of dose based on mean environmental concentrations are identified in the table as "Mean." Estimates based on the 98th percentile environmental concentrations are identified as "98th percentile."

Table 4-7. Estimated doses[a] for the "representative child"
(ng/kg-day or ng/cm^2-day).

	Inhalation	Ingestion		Dermal
		soil	vegetables	surface transfer
Isomalathion:				
Mean:	2.1	0.42	36	150
98th percentile:	2.8	1.43	123	508
OOS(O):				
Mean:	1.4	0.042	3.5	14.6
98th percentile:	2.6	0.16	13.9	58
Diethyl Fumarate:				
Mean:	b		b	7.0[c]
98th percentile:				17.5[c]

a Doses are estimated using both the mean and the 98th percentile environmental concentrations. Estimates of dose based on mean environmental concentrations are identified in the table as "Mean." Estimates based on the 98th percentile environmental concentrations are identified as "98th percentile."

Footnotes for Table 4-7 (concluded):

b Because of the nature of the toxic endpoint evaluated for diethyl fumarate (NICU), the calculation of doses via the inhalation and ingestion routes is unnecessary.

c Dosage units for diethyl fumarate are ng/cm^2-day; a surface concentration. See section 4.3.3.1.1, "Transfer from Contaminated Surfaces: Special Case" for more details.

Table 4-8. Estimated doses[a] for a child from a case of pica, surface touching (licking hands), direct malathion-bait deposition onto the skin, and swimming in contaminated water (ng/kg-day). (Special cases #1C, #4C, #2C, and #3C, respectively)

	Ingestion		Dermal	
	Soil (pica)	Bait (surface touching)	Direct Deposition	Swimming
Isomalathion:				
Mean:	1.3	103	54	76
98th percentile:	4.3	344	183	255
OOS(O):				
Mean:	0.13	10	5.2	7.1
98th percentile:	0.50	39	20.8	29.5

a Doses are estimated using both the mean and the 98th percentile environmental concentrations. Estimates of dose based on mean environmental concentrations are identified in the table as "Mean." Estimates based on the 98th percentile environmental concentrations are identified as "98th percentile."

4.4 Summation of Doses for Each "Scenario"

Estimated doses under differing sets of conditions are presented in Tables 4-5 and 4-6 for adults and Tables 4-7 and 4-8 for children. The estimated dose for each route of exposure is shown for the "representative adult" (Table 4-5); "adult special cases" (Table 4-6); "representative child" (Table 4-7); and "child special cases" (Table 4-8). The total dose of each coproduct from all exposure routes is then estimated for either age group as the summation of the doses estimated for the individual exposure routes. For example, in the case of the outdoor worker, the contribution to the total dose by the inhalation, ingestion, and the dermal routes (seen individually in Table 4-5), are summed yielding a total dose estimate for that exposure scenario. These total doses are seen in Tables 5-1 and 5-2 of the following section, for isomalathion and OOS(O), respectively.

Special case dose estimates are shown separately in Tables 4-6 and 4-8 for the adult and child, respectively; each may be folded into the appropriate scenario to arrive at a dose estimate for individuals exhibiting that particular characteristic. For example, an isomalathion dose estimate for the representative child exposed at the 98th percentile environmental concentrations who has pica and licks their hands would be: 2.8 ng/kg-day (inhalation) + 123 ng/kg-day (ingestion of vegetables) + 508 ng/kg-day (surface transfer) + 4.3 ng/kg-day (pica soil) + 344 ng/kg-day (licking hands) = 982.1 ng/kg-day or approximately 1 μg/kg-day.

5.0 Risk Characterization

With the exception of malaoxon, where the data are equivocal, there is no evidence in the scientific literature suggesting that long-term exposure to the coproducts of malathion causes cancer (DHS, 1991a). Therefore, this supplemental risk assessment includes solely an analysis of non-cancer health risks from acute exposure to the malathion coproducts.

5.1 Calculation of the Hazard Index

Non-cancer health risks associated with acute exposure to chemicals such as the malathion coproducts are evaluated by calculating the hazard index (HI). A hazard index is a means for evaluating the potential for adverse health effects from exposure to a non-carcinogenic chemical. The hazard index is calculated as the ratio of the dose to the reference exposure level (REL). The REL is a dose level, typically extrapolated from animal experiments, at which no adverse health effects are anticipated. To calculate RELs, the-no-observable-adverse-effect-levels (NOAELs) or the lowest-observable-adverse-effect-levels (LOAELs) are divided by factors of 10 (usually) until the major sources of uncertainty in the database have been considered (DHS, 1991a).

Health protection is achieved if the estimated or actual human dose of coproduct is below the relevant REL, or if the hazard index is less than one. Exposures greater than the REL (hazard index is greater than one), are not necessarily hazardous and do not absolutely result in adverse health effects. However, further examination of the public health implications of such a result is required. The acute RELs for isomalathion, OOS(O), and diethyl fumarate used in this risk assessment are 2,000 ng/kg-day, 500 ng/kg-day, and 80 ng/cm^2-day, respectively. Details of the derivation of the acute RELs for diethyl fumarate and OOS(O) can be seen in Sections 3.1 and 3.2, respectively, of this report. The REL derivation for isomalathion, discussed in Section 3.3 of this document, was originally derived for malaoxon and is found in the *1991 HRA*, Section 8.4.

Total dose estimates and the calculated hazard indices for isomalathion and OOS(O) from the various exposure pathways are presented for the scenarios and special cases in Tables 5-1 and 5-2, respectively. For example, in the case of #1 Adult, the estimated inhalation, ingestion and dermal doses are summed for a 70 kg active, outdoor worker who consumes homegrown vegetables and is outdoors for 12 hours per day to yield a total dose estimate for that "lifestyle-type," or scenario. Specifics of each scenario can be found in the text of this document as well as in the table legends. In addition, detailed discussions of individual exposure pathways and complete exposure scenarios can be found in the *1991 HRA* (Section 7; Exposure Estimation).

Table 5-1. Dose estimates[a] and hazard indices by scenario for isomalathion.

	Dose (ng/kg-day)		Hazard Index	
	Mean	98th percentile	Mean	98th percentile
#1 Adult	64	214	0.03	0.11
#1A Special	31	105	0.02	0.05
#2A Special	5.4	18.0	0.003	0.009
#1 Child	189	635	0.09	0.32
#1C Special	1.3	4.3	0.0007	0.002
#2C Special	54	103	0.03	0.09
#3C Special	76	255	0.04	0.13
#4C Special	103	344	0.05	0.17

Table 5-2. Dose estimates[a] and hazard indices by scenario for OOS(O).

	Dose (ng/kg-day)		Hazard Index	
	Mean	98th percentile	Mean	98th percentile
#1 Adult	6.9	25.7	0.01	0.05
#1A Special	3.0	11.9	0.006	0.02
#2A Special	0.5	2.0	0.001	0.004
#1 Child	19.5	74.7	0.04	0.15
#1C Special	0.13	0.50	0.0003	0.001
#2C Special	5.2	20.8	0.01	0.04
#3C Special	7.1	29.5	0.01	0.06
#4C Special	10	39	0.02	0.08

Footnote for Tables 5-1 &5-2:

a Doses are estimated using both the mean and the 98th percentile environmental concentrations. Estimates of dose based on mean environmental concentrations are identified in the table as "Mean." Estimates based on the 98th percentile environmental concentrations are identified as "98th percentile."

Legend for Tables 5-1 & 5-2:

Hazard Index. Defined as the ratio of estimated dose to reference exposure level or REL (dose/REL). The REL for OOS(O) is derived in this document (Section 3.2.6; page 18) and is 500 ng/kg-day for pulmonary morphological changes. The REL used for isomalathion is the same as that for malaoxon and is 2,000 ng/kg-day for significant AChE inhibition. Derived in the *1991 HRA.* (DHS, 1991a, Section 8.4).

#1 Adult. inhalation - "outdoor worker"; ingestion - "garden vegetables"; dermal - "very active." Identical with Adult #3 in the *1991 HRA* (Table 8-5, page 8-29).

#1A Special. Estimated dermal dose from malathion-bait deposited directly on the skin (outside during malathion-bait application). Assumptions used are outlined in the text and are the same as Special(derm)$_1$ "direct malathion-bait deposition" in the *1991 HRA*.

#2A Special. Estimated dermal dose from swimming in a contaminated pool (average depth of four feet) for one hour on the day of application. Assumptions used are outlined in the text and are the same as Special(derm)$_2$ "swimming" in the *1991 HRA*.

#1 Child. inhalation - "very active"; ingestion - "soil and garden vegetables"; dermal - "very active." Identical with Toddler #5 in the *1991 HRA* (Table 8-5; page 8-29).

#1C Special. Estimated dose from the oral ingestion of 10 grams of contaminated soil (1 cm mixing depth) due to pica behavior. Assumptions used are outlined in the text and are the same as Case(ing)$_5$ "pica" in the *1991 HRA*.

#2C Special. Estimated dermal dose from malathion-bait deposited directly on the skin (outside during malathion-bait application). Assumptions used are outlined in the text and are the same as Special(derm)$_5$, "direct malathion-bait deposition" in the *1991 HRA*.

#3C Special. Estimated dermal dose from swimming in a contaminated wading pool (six inches deep) for one hour on the day of application. Assumptions used are outlined in the text and are the same as Special(derm)$_5$ "swimming" in the *1991 HRA*.

#4C Special. Estimated ingested dose from eating, on two occasions, malathion-bait stuck on hands (265 cm^2 area) from the touching of contaminated surfaces. Assumptions used are outlined in the text and are the same as Case(ing)$_6$ "surface touching" in the *1991 HRA*.

5.2 Isomalathion and Malaoxon Estimated Doses Combined

Malaoxon and isomalathion share a common mechanism of action: inhibition of AChE. Therefore, it would be expected that the two compounds would exhibit additive toxicity when present in the malathion-bait. To evaluate the additive toxicity of these two compounds, we added the acute doses of malaoxon (DHS, 1991a) to those estimated for isomalathion in Section 4 of this document and calculated the combined hazard indices (Table 5-3). From these

calculations we can estimate the relative contribution of isomalathion to the theoretical risk for AChE inhibition from exposures to technical mixtures of malathion in the bait.

Table 5-3. Combined dose estimates and calculated hazard indices for isomalathion and malaoxon.

	Dose (ng/kg-day)		Hazard Index	
	Mean	98th percentile	Mean	98th percentile
#1 Adult:				
Inhalation	10	28	0.005	0.01
Ingestion	115	366	0.06	0.18
Dermal	298	932	0.15	0.47
Total	423	1326	0.21	0.66[a]
#1 Child:				
Inhalation	17	54	0.01	0.03
Ingestion	276	823	0.14	0.41
Dermal	800	2508	0.40	1.25
Total	1093	3385	0.55	1.69[a]

a The 98th percentile hazard indices for malaoxon alone are 0.6 (adult) and 1.4 (child). Shown in Table 8-6 of the *1991 HRA*.

Hazard Index. Defined as the ratio of estimated dose to reference exposure level or REL (dose/REL). The malaoxon REL used for this comparison was derived in the *1991 HRA* and is 2,000 ng/kg-day for significant AChE inhibition.

#1 Adult. inhalation - "outdoor worker"; ingestion - "garden vegetables"; dermal - "very active." Identical with Adult #3 in the *1991 HRA* (Table 8-6, page 8-30).

#1 Child. inhalation - "very active"; ingestion - "soil and garden vegetables"; dermal - "very active." Identical with Toddler #5 in the *1991 HRA* (Table 8-6; page 8-30).

5.3 Diethyl Fumarate

The relatively unique nature of the exposure estimation for the coproduct diethyl fumarate was discussed in Section 4.3.3.1.1. Instead of estimating a systemic dose for this compound, a dermal "surface dose" from exposure to surfaces contaminated with malathion-bait is estimated. Repeated in Table 5-4 are the "surface dose estimations" calculated for diethyl fumarate in

Section 4.3.3.1.1 of this risk assessment. Also included in Table 5-4 are the hazard indices calculated for the theoretical diethyl fumarate exposures estimated in this document, based on an acute REL of 80 ng/cm^2-day (Section 3.3). The calculation of hazard indices for this coproduct is performed by dividing the estimated doses by the acute REL. Interpretation of the hazard index for this type of exposure/toxicity, however, may not be as straightforward as with the other coproducts (see Section 6.1.3).

Table 5-4. Surface dose estimates (ng/cm^2-day)
and calculated hazard indices for
diethyl fumarate

Diethyl Fumarate (surface concentration) (ng/cm^2-day)		Mean	98th percentile
	Adult	7.8	19.4
	Child	7.0	17.5
Hazard Index:			
	Adult	0.10	0.24
	Child	0.09	0.22

Hazard Index. Defined as the ratio of the estimated dose to the reference exposure level or REL (dose/REL). The REL used for this comparison is derived for the purposes of this risk assessment and is 80 ng/cm^2-day for the production of NICU (Section 3.3.4).

6.0 Conclusions and Recommendations

6.1 Conclusions

No new significant health risks associated with the aerial application of a malathion-bait mixture are identified as a result of this risk assessment. As was the case for malathion and malaoxon in the *1991 HRA*, dermal exposure accounts for the most significant proportion of the dose, ingestion accounting for the next largest fraction, with only a minor contribution from the inhalation route.

In all cases, under all exposure conditions considered in this risk assessment, the calculated hazard indices are below 1.0 and in most cases are equal or less than 0.1, particularly when evaluating risks from the coproducts alone. The highest calculated hazard index is that for #1Child exposed to isomalathion at the 98th percentile environmental concentrations, which, when summed with all special cases, results in a hazard index of 0.73 (Table 5-1).

6.1.1 Isomalathion

Isomalathion appears to be a minor contributor to the overall AChE inhibition potential of malathion-bait, accounting for 20% or less of the combined malaoxon/isomalathion hazard index. A comparison of the isomalathion hazard index of 0.32 (#1Child, no special cases) to that for malathion (hazard index = 40.7) underscores the minor contribution made directly by isomalathion to the theoretical risk of AChE inhibition that results from exposure to malathion and/or malathion-bait mixtures. Therefore, it appears that the overall contribution by isomalathion to the theoretical risk of AChE inhibition posed by malathion-bait is negligible.

There is a great deal of uncertainty associated with our evaluation, however. Arguably, the most significant weakness in our analysis of isomalathion is in the end point chosen for evaluation. Preferably, the choice would have been potentiation of malathion toxicity via inhibition of carboxylesterases, the enzymes responsible for the detoxification of malathion. Numerous studies are available conclusively demonstrating isomalathion as a major factor in the potentiation of malathion toxicity. For example, a one percent increase in the isomalathion content (e.g., from two to three percent) of a batch of technical malathion can increase the toxicity (as measured by the rat, oral LD_{50}) by an order of magnitude with no alteration of its insecticidal properties. We are unaware of any methodologies to measure and translate "potentiation" into a quantitatively useful risk assessment. For this reason, the significant inhibition of plasma and RBC AChE is chosen as an alternate but relevant toxicological end point.

Other problems are associated with the analytical data set for isomalathion. First, as cautioned by the authors of the coproducts monitoring publication, "the [monitoring] results for isomalathion are more qualitative" (Brown *et al.*, 1993). A highly variable recovery was cited as the reason, and no additional explanation was offered. Furthermore, no air monitoring data for this coproduct are available. Therefore, for the purposes of inhalation dose estimation, air concentrations of malaoxon are used as surrogates for those of isomalathion. This substitution is

justified on the basis that the vapor pressures of these two compounds are similar (within an order of magnitude). It is also assumed that, although by different mechanisms, their relative rates of formation and degradation are similar. With these assumptions, a ratio of isomalathion to malaoxon in the air, roughly equivalent to the ratio observed in the tank mixes, would be expected. Inspection of the analytical results of 14 tank mixes used in the application revealed a isomalathion/malaoxon ratio of approximately 1.0. Because no correction or scaling is required, air concentrations of malaoxon are used directly for estimating isomalathion exposure point concentrations in air.

Even in selecting a well-characterized end point, the lack of toxicological data proved to be a source of difficulty with the assessment of this coproduct. Although a known and potent inhibitor of AChE, little quantitative toxicological data exist regarding the effect(s) of isomalathion on this enzyme. Indeed, the data pertaining to cholinesterase inhibition by isomalathion are so inadequate that it precluded the calculation of an independent REL. The REL used for the calculation of hazard indices for isomalathion exposures was originally developed for malaoxon and used in the *1991 HRA*. Considering the lack of toxicity information, the use of a malaoxon REL for isomalathion can be justified based on the similarities in chemical structure, mechanism of toxic action (inhibition of AChE), and equipotence (LD_{50}s are 113 mg/kg and 158 mg/kg for isomalathion and malaoxon, respectively). For these reasons, the acute REL for significant inhibition of plasma and RBC AChE activity by malaoxon of 2,000 ng/kg that was developed for use in the *1991 HRA* is used as the acute REL for exposure to isomalathion in this risk assessment.

6.1.2 O,O,S-Trimethyl phosphorothioate

Under all conditions of exposure assumed in our evaluation, the estimated doses of OOS(O) are below the acute REL for this compound, even considering the special case scenarios that assume upper-bound exposures resulting from a high rate of activity. Hazard indices for the "representative adult and child" exposed at the 98^{th} percentile environmental levels when summed with their special case situations are 0.07 and 0.33 for the adult (#1 Adult plus #1A and #2A specials) and child (#1 Child plus #1C, #2C, #3C and, #4C specials), respectively. Since these hazard indices are less than 1.0, no adverse health effects are expected as a result of these exposures.

In considering this characterization of risk, it is important to remember that the REL is determined for only one TAPT [OOS(O)] representing an entire class of compounds. It is possible that the REL for [OOS(O)] might be either less protective, or more protective, than an REL specifically derived for another individual chemical in this class of compounds. When an individual is exposed to TAPTs in malathion solutions, there is concomitant exposure to other TAPTs [for example, OSS(O)] which has comparable toxicity to OOS(O)]. Other TAPTs are also present that are either less toxic and/or antagonize the toxicity of the more toxic TAPTs [for example, OOO(O)]. Existing data are insufficient to refine the risk characterization of TAPTs.

6.1.3 Diethyl Fumarate

For diethyl fumarate, the estimated "worst-case" topical dose is only one-quarter of the acute REL and no adverse health effects would be expected to occur from exposure to this coproduct. This dose estimation used in the risk assessment yields an approximate average concentration across the entire surface of the skin and does not factor in the possibility for the existence of localized areas of high and low concentrations. Theoretically, localized concentrations greater than the REL could exist from direct dermal contact with the malathion-bait and a toxic response (i.e., NICU) observed.

The method of averaging dermal exposures across the total body surface may not be appropriate for this coproduct considering the sticky, molasses-like matrix. Complaints of skin rashes following a malathion-bait application were frequently associated with individuals trimming hedges. If all of the malathion-bait that deposited onto vegetation adhered, and 50 to 100% of the malathion-bait is transferred to the hands and arms of an adult (surface area of 3,240 cm^2) engaged in trimming, a dose exceeding the REL might be received by trimming a hedge 6 to 12 linear feet long and two feet wide. Even if the transfer to skin is less than 50% it would not require an unusually long hedge (greater than 2 feet by 12 feet) to deliver a localized dose to the skin surface of the hands in excess of the REL. Of course, other possibilities such as the effects of diethyl fumarate exacerbated by the presence of the protein bait, malathion itself, or other currently unknown factors must still be considered as potentially related to skin rashes following the application of malathion-bait.

6.2 Recommendations

In our risk assessment we incorporated health-conservative assumptions where there were recognized inadequacies in the toxicology and environmental monitoring data bases. Validation of the conclusions of this risk assessment and improvement of our knowledge of the potential human health risks associated with malathion-bait applications would be advanced by the implementation of the following recommendations:

(a) Improvement in analytical methodologies, particularly those needed for isomalathion monitoring, is important, as they are one of the most significant limiting factors in this risk assessment. Once the analytical methodology is improved, additional isomalathion monitoring to confirm or to modify the conclusion(s) of this report should be considered.

(b) Repeating the monitoring of diethyl fumarate on surfaces over a longer time period is suggested. Surface concentrations of this analyte continued to increase over the course of the monitoring activities. In some cases, surface levels showed no evidence of tapering off, even after nine days. Air levels also persisted for some time after the application.

(c) Both surface and air monitoring for all analytes over a longer time frame with particular emphasis on repeated applications in order to estimate subchronic and/or chronic doses should be considered.

(d) Continue routine monitoring of malathion product and tank mixtures for the purposes of quantifying isomalathion. In accordance with the WHO recommendation, technical mixtures with isomalathion at levels exceeding 1.8% of the nominal malathion content should be rejected and returned.

(e) Close attention should be paid to the emerging toxicological literature as it pertains to malathion coproducts. This is especially important with respect to the trialkyl phosphorothioate class of coproducts because of the nature of the toxicity associated with exposure to these compounds (i.e., changes in lung morphology and fetal deaths in experimental animals). Since respiratory problems have been reported in malathion-bait exposed human populations, additional studies (toxicological, epidemiological, mechanistic) concerning the possible role of this class of coproducts in the etiology of these respiratory problems should be considered.

(f) Risk assessment methodologies pertaining to surface dose estimation should be reviewed and if necessary refined. Applicable research of surface to surface transfer rates, surface distribution profiles, and other exposure-related variables is important in order to more accurately evaluate the toxic potential of exposure to locally acting, topically active agents. Additional areas for research may be identified during routine literature reviews.

(g) Information concerning the environmental persistence and fate of all coproducts would be important to derive a more realistic estimate of chronic human exposure to malathion coproducts. Studies regarding the environmental behavior of these compounds would help to reduce the uncertainty in chronic exposure assessment.

(h) Exposure to malathion coproducts over a period of several days to weeks due to repeated bait applications over the same area(s) is plausible. A greater understanding of the longer term toxicities of the coproducts would aid the evaluation of potential risks from this type of exposure. There are few sub-chronic and chronic toxicity tests for the coproducts of malathion; results from such studies would be helpful to characterize the risks of repeated exposure to these compounds.

7.0 References

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8.0 Glossary

dermal absorption: The process by which a substance is transported across the skin barrier and into the living tissue of the body. Synonymous with dermal uptake.

diethyl fumarate: A malathion coproduct present in technical mixtures of the pesticide. Human exposure to diethyl fumarate can result in a condition known as non-immunologic contact urticaria (NICU), a reaction consisting of erythema and edema that appears approximately 5 to 60 minutes after skin contact. This coproduct is possibly involved in the etiology of skin rashes subsequent to malathion-bait applications.

environmental fate: The destiny of a chemical or pollutant after its release into the environment.

exposure medium: Any one of the basic categories of material surrounding or contacting an organism (e.g., air, water, soil, sediment, etc.) through which chemical pollutants can move and reach the organism.

exposure parameters: A set of criteria that serve to define the quantifiable aspects of a "lifestyle" and by doing so, determines the potential exposure of a receptor (e.g., "swimming for ***one*** hour in contaminated water")

exposure pathway: The course a chemical takes from its source, or point of release into the environment, to the exposed organism(s).

exposure point: A location of potential contact between an organism (receptor) and a chemical.

exposure point concentration: The concentration of chemical at the point of contact with a receptor. Typically associated with an environmental medium and reported as "air concentration" or "soil concentration" or in similar units.

hazard index: A measure of the non-carcinogenic risk from exposure to a chemical. Defined as the ratio: reference exposure level (REL)/estimated dose; a hazard index of less than one implies a lack of risk from exposure to a chemical at or below the estimated dose level. A hazard index greater than one may or may not mean the given exposure is risky.

health-conservative: Describes assumptions made for risk assessment purposes that, if in error, will tend to overestimate the theoretical human risk from exposure to a substance providing additional margin of safety.

health-protective: Synonymous with "health-conservative."

isomalathion: A highly toxic malathion coproduct, with toxic properties similar to those of malaoxon. A major determinant of the acute toxicity of

	technical mixtures of malathion.
malaoxon	Both a metabolite and coproduct of malathion, responsible for the insecticidal activity and toxicity of malathion via the inhibition of cholinesterase(s).
malathion:	An insecticide belonging to the organophosphate (OP) class of pesticides. The active ingredient of the malathion-bait mixtures used for Medfly control and is known for its low mammalian toxicity.
maximally exposed individual (MEI):	The hypothetical individual, found in risk assessments performed according to "Superfund" guidelines, whose lifestyle (scenario) results in their receiving the maximum exposure to a chemical according to a scenario defined by realistic exposure parameters.
OOS(O):	Abbreviation for O,O,S-trimethyl phosphorothioate, a member of the TAPTs group of malathion coproducts, exposure to which is quantitatively evaluated in this document.
pica:	A behavior, typically seen in children, defined as an abnormal craving to eat substances not fit for food (e.g., soil, paint, clay).
receptor:	In the present case, this is an individual exposed to malathion coproducts.
reference exposure level (REL)	The reference exposure level (REL) is a dose level, typically extrapolated from animal experiments, at which no adverse health effects are anticipated.
surface dose:	The dose or amount of a substance presented to an organism prior to absorption. The percent of the surface dose absorbed is known as the internalized or systemic dose.
surrogate data:	Substitute data or measurements on one substance used to estimate analogous or corresponding values of another substance.
TAPTs:	An abbreviation for "trialkyl phosphorothioate(s)" that is used throughout this document.
trialkyl phosphorothioates:	A group of malathion coproducts present in technical mixtures of the pesticide. An important member of this class of coproducts, OOS(O), can cause an unusual, delayed pulmonary toxicity in laboratory animals, a syndrome that is typically fatal.